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- poranic acid derivativas, processes for their preparation, phermaceutical ositions containing them; their starting compounds and their proparation.
- (3) 7-scylamino-3-substituted cephelosporanic acid deriva-tives of the formula:

R⁴ is lower alkyl and

R³ is smine or a protected amine group, 557 R2 is lower alkoxymathyl, lower alkylthiomethyl or lower sikenyithiomethyl, R' is carboxy or a protected carboxy group, and A is lower alkylene which may have certain substi-

and pharmaceutically acceptable self thereof and pro-Cresses for their preparation and also a pharmacautically composition comprising, as an affective ingredient, the

above compound in association with pharmacautically acceptable carriars. The invention also relates to the starting 769

7- ACYLAMINO - 3- SUBSTD

CEPHALOSPORIN DERIVS. + USEFUL

ANTIBACTERIALS IN HUMAN A.S

AND VETERINARY MEDICING

CH₂S-R^D.

TITLE from page

7-ACYLANINO-3-SUBSTITUTED CEPHALOSPORANIC, ACID DENINATIVES, PROCESSES FOR THEIR PREPARATION PHRINACEUTICAL COPPOSITIONS CONTAINING THEN AND THEIR STARTING COPPONEN The present invention relates to novel 7-scylamino-J-substituted cephalosporanic acid derivotives and pharmaccutically acceptable salts thereof.

More particularly, it relates to novel 7-acylamino-3-substituted combalosporantic acid derivatives and pharmaceutically acceptable saits thereof, which have, antinicrobial activity, to processes for the preparation thereof, to a pharmaceutical composition comprising the same, and to a method of using the same therapeutically in the treatment of infectious diseases in human being and aniams.

Accordingly, one object of the present invention is to provide move 7-acylamino-3-substituted cephalos-poranic acid derivatives and pharmaceutically acceptable

salts thereof, which are highly active against a number antimicrobial agents, especially oral administration, of pathogenic microorganisms and are useful as

acylamino-3-substituted cephalosporanic acid derivatives Another object of the present invention is to 5 provide processes for the preparation of novel 7and salts thereof.

cephalosporanic acid derivatives and pharmaceutically A further object of the present invention is to provide a pharmaceutical composition comprising, as active ingredients, said 7-acylamino-3-substituted acceptable salts thereof.

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Still further object of the present invention is to provide a method of using said 7-acylamino-3-substituted acceptable salts thereof in the treatment of infectious cephalosporanic acid derivatives and pharmaceutically diseases by pathogenic microorganisms in human being and animals, The object 7-acylamino-3-substituted cephalosporanic 20 acid derivatives are novel and can be represented by the following general formula:

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$$R^{1-A-CONH} \longrightarrow R^{2} \qquad (1)$$

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wherein R⁴ is lower alkyl and
R⁵ is amino or a protected amino group,

R² is lower alkoxymethyl, lower alkylthiomethyl or lower alkenylthiomethyl,

R³ is carboxy or a protected carboxy group, and

"NOR6, wherein R6 is hydrogen, lower alkenyl, lower alkynyl, lower alkyl or lower alkyl subof amino, a protected amino group, hydroxy, stituted by one or more substituent(s) segroup, amino, a protected amino group, and is lower alkylene which may have a substituent selected from the groups consisting lected from carboxy, a protected carboxy oxo and a group of the formula; heterocyclic group.

also included within the scops of the present invention. and double bond in those molecules and such isomers are In the object compounds (I) and the corresponding mentioned below, it is to be understood that there may be one or more stereoisomeric pair(s) such as optical and geometrical isomers due to asymmetric carbon atom starting compounds (II) to (IV) in Processes 1

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compounds and the starting compounds, it is to be noted isomer means one geometrical isomer having the partial isomer, anti isomer and a mixture thereof, and the syn With regard to geometrical isomers in the object means a group of the formula: "C=NAOR", include syn that, for example, the object compounds, wherein A structure represented by the following formula:

, wherein R and R are each as defined and the anti isomer means the other geometrical isomer having the partial structure represented by the followabove, ing formula:

$$R^+ \cdot C^-$$
 , wherein R^1 and R^6 are each as defined $R^6 \cdot o \cdot N$

Regarding the other object and starting compounds as mentioned above, the syn isomer and the anti isomer

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can also be referred to the same geometrical isomers as illustrated for the compounds (I).

- salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, and may include a salt with a base or an acid addition Suitable pharmaceutically acceptable salts of the object compounds (I) are conventional non-toxic salts magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt
- ethanolamine salt, triethanolamine salt, dicyclohexylamine (e.g. triethylamine salt, pyridine salt, picoline salt, sait, N,N'-dibenzylethylenediamine salt, etc.; etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic

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- carboxylic or sulfonic acid addition salt (e.g. formate, a salt with a basic or acidic amino acid (e.g. arginine, sulfonate, benzenesulfonate, p-toluenesulfonate, etc.); acetate, trifluoroacetate, maleate, tartrate, methaneaspartic acid, glutamic acid, etc.); an intermolecular 5 20
- The said intermolecular quaternary salt can be formed n case that the heterocyclic group in R 6 in the compounds (I) contains nitrogen atom(s) (e.g. pyridy1, or intramolecular quaternary salt, and the like. S
 - may include 1-lower alkylpyridinium lower alkylsulfate pyridinium ethylsulfate, etc.), 1-lower alkylpyridinium case that heterocyclic group in R⁶ in the compounds (I) halide (e.g. 1-methylpyridinium lodide, etc.) and the like. The said intramolecular salt can be formed in R 3 is carboxy, and suitable intramolecular salt may etc.), and suitable intermolecular quaternary salt contains nitrogen atom(s) (e.g. pyridyl etc.) and include 1-lower alkylpyridinium carboxylate (e.g. 1-methylpyridinium carboxylate, 1-ethylpyridinium [c.g. 1-methylpyridinium methylsulfate, 1-ethyl-

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- 1-isopropylpyridinium carboxylate, 1-butylpyridinium carboxylate, 1-propylpyridinium carboxylate, carboxylate, etc.); and the like
- According to the present invention, the object compounds (I) and the pharmaceutically acceptable salts thereof can be prepared by the processes as illustrated by the following reaction schemes.

the amino group or a salt thereof or its reactive derivative at E

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or a salt thereof

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continued to the next page)

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or a salt thereof

or a salt thereof

or a salt thereof

or a salt thereof

(I-a)

10 (3) Process 3:

(q-1)

(7) Process 7;

Removal of R²-A-CONH S R²
the aminoprotective group for R³
R³

Ra-A-CONH

 $x^{1} \cdot CH_{2} co A^{\frac{1}{2}} co M^{\frac{1}{2}} co M + \sum_{i=1}^{N} \sum_{j=1}^{N} \frac{H_{2} N^{-j} \cdot F_{1} R^{2}}{\frac{1}{3}} (y) \frac{K^{2} - k_{3}^{2}}{\frac{1}{3}} A^{\frac{1}{3}} co M + \sum_{i=1}^{N} \frac{1}{3} K^{2}$

or a salt thereof

or a salt thereof

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or a salt thereof

or a salt thereof

(1-e)

(5) Process 5:

(1-f)

(continued to the next page)

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R¹-A-CONH R² Introduction of R¹-A-CONH P the carboxy.

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or a salt thereof

or a salt thereof

(1V)

or a salt thereof

or a salt thereof

(I-c)

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(4) Process 4:

(I-d)

(8) Process 8:

Removal of R¹-A-COM State of Random Particles Random State Random Rand

R¹-A-CONH

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(2) Process 2;

(6) Process 6;

R¹-A³-CONHTTS Reduction R¹-A⁴-CONHTS N²-R²

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or a salt thereof

or a salt thereof

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(1-f)

å

R1-A6-CONH R2

or a salt thereof

30 R¹-A¹⁰-CONH
$$\longrightarrow$$
 2 (R¹)₂SO₄ (VII) R¹-A¹¹-CONH \longrightarrow 0

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R1-A12-00N1 S

R1-A11-CONH

or a salt thereof

or a salt thereof

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or a salt thereof

wherein
$$R^{B}$$
 is a protected amino group,

$$\frac{1}{\sqrt{4}}$$
 or $\frac{1}{\sqrt{4}}$

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$$H_2N + \frac{N}{4}$$
 or $H_2N + \frac{N}{4}$ or $H_2N + \frac{N}{4}$ is a protected carboxy group, H_2^k is lower alkoxycarbonyl substituted by

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or a salt thereof

$$R$$
 is lower alky1,
$$A^{l}$$
 is lower alkylene having a protected amino group,

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or a salt thereof

35 or a salt thereof

1-9

(1-1)

779 7

- 70 -

 A^6 is lower alkylene having a group of the formula: "N^OR $_0^6$, wherein R_0^6 is lower alkyl

substituted by a protected carboxy group,

is lower alkylene having a group of the formula: "N-OR 6 , wherein R_b^6 is lower alkyl

substituted by carboxy,

a group of the formula "NvOR6", wherein

R⁶ is as defined above,

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in which \mathbb{R}^A is amino or a protected amino group,

X is -S- or -SO-, and Rb' is lower alkenyl,

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R3 is as defined above, and a salt thereof.

the same as those exemplified for the object compounds (I). Suitable salts of the above starting compound are The starting compound thus formulated and other starting compounds can be

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protected amino and protected carboxy groups

or lower alkyl substituted by protected

amino and protected carboxy groups,

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alkoxycarbonyl(lower)alkyl substituted by

 A^8 is lower alkylene having a group of the formula: "N^OR $_{\text{C}}^6$, wherein $_{\text{R}}^6$ is lower

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is lower alkylene having a group of the formula: "NAOR $^6_{\rm d}$, wherein ${\rm R}^6_{\rm d}$ is lower alkoxy-

carbony1(lower)alky1 substituted by amino and carboxy or lower alkyl substituted by

continued to the next page)

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'n

substituted by a group of the formula:

All is lower alkylene having a group of the

formula: "NAOR6, wherein R6 is lower alkyl

A 10 is lower alkylene having a group of the

amino and carboxy,

formula: =N~ORf, wherein Rf is lower alkyl

substituted by a group of the formula;

A¹² is lower alkylene having a group of the formula: "N-OR $_0^4$, wherein R_0^8 is lower alkyl substituted by a cation of the formula: $\not=$

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wherein R' is as defined above, and

(IV) used in Processes 1 : and 7 are new and can be

Some of the starting compounds (II), (III) and

x^l is halogen.

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(8) Process B: Preparation of some of the starting

compounds (III)

R1-A3-RC

(III-a)

prepared, for example, from the known compounds by the methods in the following reaction schemes, and others can be prepared in a similar manner thereto or in a conventional manner.

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or a salt thereof

(III-b)

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Introduction of the group (Process B-3)

amino-protective

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(111-c)

Ra-A2-RC

(Process B-2)

Reduction

R1-A13-RC

or a salt thereof

(Process B-1) | R⁶ONH₂ (1X)

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or a salt thereof

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$$R_b^{1/4} A^2 \Omega \Omega H$$
 (III-g) or a sult thereof

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Removal of the Carboxy-protective

Removal of the carboxy-protective group (Process B-5)

or a salt thereof

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(J-111)

R. - A - RC

 $\mathtt{R}_{\mathrm{a}}^{1}\text{-}\mathtt{A}^{1}\text{-}\mathtt{R}^{\mathsf{C}}$

(D-111)

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(C) Process C: Preparation of some of the starting compounds (IV)

(IV-a)

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or a salt thereof

(II-f)

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or a salt thereof

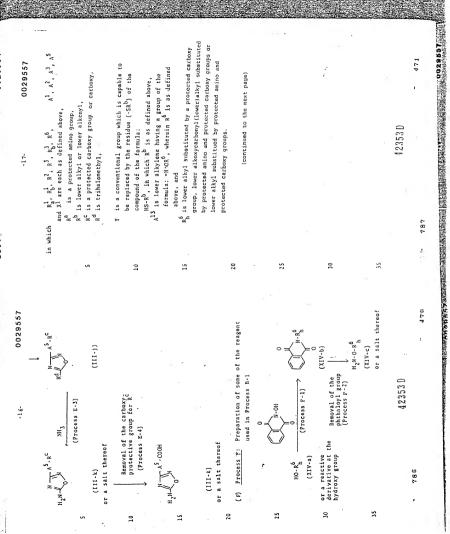
(II-g)

(1111-1)

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R

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prosent specification, suitable examples and illustration of the various definitions to be included within the In the above and subsequent description of the scope thereof are explained in detail as follows.

alkoxy such as methoxymethyl, ethoxymethyl, propoxymethyl, the like, in which the preferred one is $C_1 \cdot C_5 a l k_0 x y_m e t h y l$.

methyl group substituted by straight or branched lower isopropoxymethyl, pentyloxymethyl, hexyloxymethyl, and

Suitable "lower alkoxymethyl" group may include a

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a methyl group substituted by straight or branched lower

propylthiomethyl, isobutylthiomethyl, pentylthiomethyl,

alkylthio such as methylthiomethyl, ethylthiomethyl,

hexylthiomethyl, and the like, in which the preferred

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one is C,-C,alkylthiomethyl.

Suitable "lower alkylthiomethyl" group may include

The term "lower" in the present specification is intended to mean a group having 1 to 6 carbon atoms, unless otherwise indicated.

isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, Suitable "lower alkyl" group may include straight hexyl and the like, in which the preferred one is or branched one such as methyl, ethyl, propyl, C1-C3a1ky1.

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and the like, in which the preferred one is $\mathsf{C}_2 extsf{-}\mathsf{C}_\mathsf{S}$ alkenyl. Suitable "lower alkynyl" group may include straight Suitable "lower alkenyl" group may include straight 1-(or 2- or 3- or 4- or 5-)hexenyl, 2-methyl-2-propenyl, 1-(or 2- or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, or branched one such as vinyl, 1-propenyl, allyl,

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alkenylthio such as vinylthiomethyl, lipropenylthiomethyl,

allylthiomethyl, 2-methyl-2-propenylthiomethyl,

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1-(or 2- or 3-)butenylthiomethyl, 1-(or 2-'or 3- or 4-)-

pentenylthiomethyl, 1-(or 2- or 3- or 4-)hexenylthio-

methyl, and the like, in which the preferred one is

a methyl group substituted by straight or branched lower

Suitable "lower alkenylthiomethyl" group may include

and the like, in which the preferred one is C_2 - C_5 alkynyl. 2-(or 3- or 4-)pentynyl, 2-(or 3- or 4- or 5-)hexynyl, or branched one such as propargyl, 2-(or 3-)butynyl,

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continued to the next page)

amino group substituted by a conventional amino-protective

Suitable "protected amino group" may include an

C2-C5alkenylthiomethyl.

compounds, for example, acyl as mentioned below, mono-

or di or tri)phenyl(lower)alkyl (e.g. benzyl,

group which is used in penicillin and cephalosporin

benzhydryl, trityl, etc.), lower alkoxycarbonyl(lower)methylene (e.g. dimethylaminomethylene, etc.), etc. carbony1-1-propen-2-y1, etc.), di (lower) alkylaminoalkylidene or its enamine tautomer (e.g. 1-methoxy-

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Suitable "acyl" may include an aliphatic acyl, an aromatic acyl, a heterocyclic acyl and an aliphatic ຄ

acyl substituted with aromatic or heterocyclic group(s). unsaturated, acyclic or cyclic ones, such as lower The aliphatic acyl may include saturated or

isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, alkanoyl (e.g. formyl, acetyl, propionyl, butyryl,

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erc.), lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, etc.), lower alkoxycarbonyl (e.g. butoxycarbonyl, tert-butoxycarbonyl, etc.), lower methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,

alkenoyl (c.g. acryloyl, methacryloyl, crotonoyl, etc.), $(C_{\mathfrak{q}}-C_{\mathfrak{p}})$ -cycloalkanecarbonyl (e.g. cyclohexanecarbonyl, etc.), amidino, and the like.

toluoyl, xyloyl, etc.), arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.), and the like.

The aromatic acyl may include aroyl (e.g. benroyl,

carbonyl (e.g. furoyl, thencyl, nicotincyl, isonicoti-The heterocyclic acyl may include heterocyclenoyl, thiazolylcarbonyl, thiadiazolylcarbonyl,

The aliphatic acyl substituted with aromatic group(s) phenylpropionyl, phenylhexanoyl, etc.), phenyl(lower)carbonyl, etc.), phenoxy(lower)alkanoyl (e.g. phenoxyalkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxymay include phenyl(lower)alkanoyl (e.g. phenylacetyl, tetrazolylcarbonyl, etc.), and the like. 50

The aliphatic acyl substituted with heterocyclic group(s) may include thienylacetyl, imidazolylacetyl, thiadiazolylacetyl, thienylpropionyl, thiadiazolyly furylacetyl, tetrazolylacetyl, thiazolylacetyl, acetyl, phenoxypropionyl, etc.), and the like.

isopropylthio, butylthio, pentylthio, hexylthio, etc.), fluorine), lower alkoxy (e.g. methoxy, ethoxy, propoxy, hexyl, etc.), halogen (e.g. chlorine, bromine, lodine, These acyl groups may be further substituted with (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, isopropoxy, butoxy, pentyloxy, hexyloxy, etc.), lower one or more suitable substituents such as lower alkyl substituent(s) may be mono (or di or tri)halo(lower)nitro and the like, and preferable acyl having such alkylthio (e.g. methylthio, ethylthio, propylthio, propionyl; and the like..

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ilkanoyl (e.g. chloroacetyl, bromoacetyl, dichloroacetyl, carbonyl, methoxybenzyloxycarbonyl, etc.), and the like. trifluoroacetyl, etc.), mono (or di or tri)halo(lower)aethoxycarbonyl, 2,2,2-tri-chloroethoxycarbonyl, etc.), carbonyl (e.g. nitrobenzyloxycarbonyl, chlorobenzyloxyalkoxycarbonyl (e.g. chloromethoxycarbonyl, dichloronitro (or halo or lower alkoxy)phenyl(lower)alkoxy-

Suitable "protected carboxy group" may include an esterified carboxy group which is conventionally used in penicillin or cephalosporin compounds at their 3rd 10

group" may include lower alkyl ester (e.g. methyl ester, Suitable "ester moiety" in "esterified carboxy or 4th position thereof,

ethyl ester, propyl ester, isopropyl ester, butyl ester, ester (e.g. ethynyl ester, propynyl ester, etc.), lower pentyl ester, hexyl ester, etc.), lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.), lower alkynyl alkoxy(lower)alkyl ester (e.g. methoxymethyl ester, isobutyl ester, t-butyl ester, pentyl ester, tert-2

substituted lower alkyl ester (e.g. 2-amino-2-carboxyethoxymethyl ester, isopropoxymethyl ester, 1-methoxyisopropylthiomethyl ester, etc.), amino- and carboxysster, ethylthiomethyl ester, ethylthioethyl ester alkylthio(lower)alkyl ester (e.g. methylthiomethyl ethyl ester, 1-ethoxyethyl ester, etc.), lower 25

(or di or tri)phenyl (lower)alkoxycarbonyl substituted lower alkyl ester such as lower alkoxycarbonylamino and monoprotected amino and protected carboxy substituted lower ethyl ester, 3-amino-3-carboxypropyl ester, etc.),

2,2,2-trichloroethyl ester, etc.), lower alkanoyloxy(lower)benzhydryloxycarbonylethyl, 3-tert-butoxycarbonylamino--benzhydryloxycarbonylpropyl, etc.), mono(or di or tri)halo(lower)alkyl ester (e.g. 2-iodocthyl ester, alkyl ester (e.g. 2-tert-butoxyc.rbonylamino-2. 20

alkyl ester (e.g. accesymethyl ester, prophonylony esteryl ester, buyrzydognethyl estery, isobuyrzhony esteryl esterylyndognethyl esterylyndogneth

2-propionyloxyethyl ester, l-acetoxypropyl ester, etc.), lower alkansulfonyl(lower)alkyl ester (e.g. mexylachyl ester, e.c.), anon odd or tri)phenyl(lower)alkyl ester, etc.), anon for or nore suitable substituent(s) (e.g. benzyl ester, 4-

- methoxybenryl ester, 4-nitrobenryl ester, phenethyl
ester, bennydryl ester, trityl ester, bels(methoxybenryl)methyl ester, 3,4-dimethoxybenryl ester, 4-bydroxy-3,5d1--burybenryl ester, etc.), aryl ester which may have
one or more suitable substituents (e.g. phenyl ester,

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15 tolyl ester, t-buylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, salicyl ester, etc.), heterocyclic ester (e.g. phthalidyl ester, etc.) and the like.

Suitable "lower alkylene" group may include straight or branched one such as methylene, ethylene, trimethylene, propylene, tetramethylene, have energylene, and the like, in which the preferred one is $C_1 \subset C_2$ alkylene and the most preferred one is methylene.

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Suitable "heterocyclic" group may include saturated or unsaturated, nonecyclic or polycyclic heterocyclic sgroup containing at least one hetero-atom such as m oxygen, gulfur, nitrogen atom and the like.

And, especially preferable heterocyclic group may be heterocyclic group such as

unsiturated 3 to 4-membered(more preferably 5 or 6-membered)baceromonocylic group containing 1 pyrolinyli, pyrolinyli, inidezolyl, pyraeolyl, pyridyl and its N-oxide, dibydropyridyl, pyriadilnyl, pyrainiyl, pyridatinyl, pyridatinyl, pyridatinyl, pyridatinyl, pyridatinyl, pyridatinyl, triazolyl (e.g. 4H-1,2,4-triazolyl,

HH-1,2,3-triazoly1, 2H-1,2,3-triazoly1, etc.),
tetrazoly1 (e.g. JH-tetrazoly1, 2H-tetrazoly1, etc.)
tc.:

saturated 3 to 8-membered(more preferably 5 or 6membered)heteremonocytis group containing 1 to 4 hittogen atom(s), for example, pyrrolidiny, imidazolidiny, piperidino, piperaziny, etc.:

unseturated condensed heterocyclic group containing
1 to 4 nitrogen atom(s), for example, indolyl,
10 isoindolyl, indolizinyl, benimiaidarolyl, quinolyl,

isoquinoly1, indazoly1, benzotriazoly1, etc.;
unsaturated 3 to 8-membered(more preferally 5 or 6membered)heteromonocyclic group containing 1 to 2

oxygen atom(s) and 1 to 3 nitrogen atom(s), for 11s example, oxatoly1, isoxatoly1, oxadiatoly1 (e.g. 1,7,4-oxadiatoly1, 1,3,4-oxadiatoly1, 1,7,5-oxadiatoly1, etc.), etc.)

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 coxyeen stool(3) and 1 to 1 mithogram services.

oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.; unsaturated condensed heterocylic around

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, bentoxatolyl, bentoxatdatolyl, etc.;

wursaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur acong 5 and 1 to 3 introgen acong 5), for example, thistolyl, isothiatolyl, thiadiatolyl (e.g. 1, 2, 4-thiadiatolyl, 1, 2, 4-thiadiatolyl, 1, 3, 5-thiadiatolyl, 1, 3, 5-thi

dihydrothiarinyl, etc.
saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to
2 sulfur atom(5) and 1 to 3 nitrogen aron(s), for

35 example, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6sulfur atom(s), for example, thienyl, dihydrodithiinyl, membered) heteromonocyclic group containing 1 to 2

unsaturated 3 to 8-membered (more preferably 5 or 6unsaturated condensed heterocyclic group containing for example, benzothiazolyl, benzothiadiazolyl, etc.; l to 2 sulfur atom(s) and l to 3 nitrogen atom(s),

unsaturated 3 to 8-membered (more preferably 5 or 6membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.; ន

unsaturated condensed heterocyclic group containing membered) heteromonocyclic group containing an oxygen arom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing l to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc. and the like.

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Thus defined heterocyclic group may optionally be substituted by one to ten, same or different, lower alkyl (e.g. methyl, ethyl, etc.); suitable substituent(s) such as:

cyclo(lower)alkenyl (e.g. cyclohexenyl; cyclohexadienyl, lower alkoxy (e.g. methoxy, ethoxy, propoxy, etc.); lower alkylthio (e.g. methylthio, ethylthio, etc.); etc.); hydroxy; halogen (e.g. chloro, bromo, etc.); (lower)alkyl (e.g. cyclopentyl, cyclohexyl, etc.); lower alkylamino (e.g. methylamino, etc.); cycloamino; protected amino as aforementioned; cyano; 25 ဗ္က

Suitable "lower alkoxycarbonyl(lower)alkyl" group (e.g. aminomethyl, aminoethyl, etc.); and the like. sulfo; sulfamoyl; imino; oxo; amino(lower)alkyl

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nitro; carboxy; protected carboxy as aforementioned:

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may include ethoxycarbonylmethyl, propoxycarbonylmethyl, Suitable "lower alkoxycarbonyl" moiety may include or 2-ethoxycarbonylethyl, and the like.

Suitable "halogen" may include chloro, bromo, iodo, ethoxycarbonyl, propoxycarbonyl, and the like.

formula: HS-R^{b.} may include halogen as exemplified above. Suitable "conventional group which is capable to be replaced by the residue $(-S-R^{\mathsf{b}})$ of the compound of the and the like.

(continued to the next page)

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Suftable "trihalomethyl" may include trichloromethyl, and the like.

Particularly, the preferred embodiment of the symbols "R1-A-", "R2" and "R3" of the object compounds (I) can be represented as follows.

The symbol "R1-A-" can be represented by the formulae:-

Rl is a group of the formula:

(e.g. chloroacetamido, dichloroacetamido, acetamido, propionamido, etc.) or monoor di- or trihalo(lower)alkanamido lower alkunamido (e.g. formamido, trifluoroacetamido, etc.)),

or 2- carboxyethyl, 1- or 2- or 3- carboxypropyl, carboxy(lower)alkyl (e.g. carboxymethyl, 1-R6 is lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, etc.), etc.), or

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methyl, ethoxycarbonylmethyl, tert- butoxycarbonylmethyl, lower alkoxycarbonyl(lower)alkyl (e.g. methoxycarbonylbenzyloxycarbonylmethyl, benzhydryloxycarbonylmethyl, tert- butoxycarbonylethyl, etc.) or mono- or di- or esterified carboxy(lower)alkyl (more preferably triphenyl(lower)alkoxycarbonyl(lower)alkyl (e.g. benzhydryloxycarbonylethyl etc.)); or

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R1-A- , in which 0

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R1 is a group of the formula:

wherein R5 is amino or acylamino (more preferably lower alkanamido (e.g. formamido,

scetamido, propionamido, etc.)], and

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tert- butoxycarbonylaminomethylene, etc.)], hydroxymethylene methoxycarbonylaminomethylene, ethoxycarbonylaminomethylene, A is methylene, aminomethylene, acylaminomethylene (more preferably lower alkoxycarbonylaminomethylene (e.g. or carbonyl; or 15

- 3 R1-A- , in which
- Rl is a group of the formula:

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propyl, isopropyl, butyl, pentyl, etc.), and wherein R4 is lower alkyl (e.g. methyl, ethyl,

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lower alkoxycarbonylaminomethylene (e.g. methoxycarbonylaminomethylene, ethoxycarbonylaminomethylene, tert- butoxycarbonyl-A is aminomethylene or acylaminomethylene (more preferably uminomethylene, etc.)].

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the symbol "R2" can be represented by:-

lower alkoxymethyl (e.g. methoxymethyl, ethoxymethyl, 32

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lower alkenylthiomethyl (e.g. vinylthiomethyl, allylthiomethyl, lower alkylthiomethyl (e.g. methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, etc.); or propoxymethyl, isopropoxymethyl, etc.); butenylthiomethyl, etc.).

The symbol "R3" can be represented by :-

alkoxycarbonyl (e.g. benzyloxycarbonyl, benzhydryloxycarbonyl, carboxy or esterified carboxy (more preferably lower alkoxybutoxycarbonyl, etc.) or mono- or di- or triphenyl(lower)-. The processes 1 to 13 for the preparation of the carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, tertphenethyloxycarbonyl, etc.)],

object compounds (I) of the present invention are explained in detail in the following. (1) Process 1:

at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt The compounds (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative

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(III) may include the same ones as illustrated for the Suitable salts of the starting compounds (II) and Compounds (I)

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Suitable reactive derivative at the carboxy group of hyde, benzaldehyde, salicylaldehyde, phenylacetaldehyde, as an aldehyde compound (e.g. acetaldchyde, isopentaldeaction of the amino group with a carbonyl compound such the compound (II) may include a conventional one, for example, a silyl derivative formed by the reaction of chlorobenzaldehyde, hydroxynaphthoaldchyde, furfural, its tautomeric enamine type isomer formed by the rethe compound (II) with a silyl compound such as bis-(trimethylsilyl)acetamide, trimethylsilylacetamide, etc.; isocyanate; isothiocyanate; Schiff's base or p-nitrobenzaldehyde, m-chlorobenzaldehyde, p-

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ketone, acetylacetone, ethyl acetoacetate, etc.), and (e.g. acetone, methyl ethyl ketone, methyl isobutyl thiophenecarboaldehyde, etc.) or a ketone compound

- Suitable reactive derivative of the compound (III) anhydride, an activated amide, an activated ester, and bromide; a mixed acid anhydride with an acid such as the like, and preferably an acid chloride and acid may include, for example, an acid halide, an acid
 - dibenzylphosphoric acid, halogenated phosphoric acid, acid, phenylphosphoric acid, diphenylphosphoric acid, substituted phosphoric acid (e.g. dialkylphosphoric thiosulfuric acid, sulfuric acid, alkyl carbonate etc.), dialkylphosphorous acid, sulfurous acid, 2
 - aromatic carboxylic acid (e.g. benzoic acid, etc.); 2-ethylbutyric acid, trichloroacetic acid, etc.), carbonate, etc.), aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, (e.g. methyl carbonate, ethyl carbonate, propyl 13
- with a heterocyclic compound containing imino function a symmetrical acid anhydride; an activated acid amide dimethylpyrazole, triazole or tetrazole; an activated ester (e.g. p-nitrophenyl ester, 2,4-dinitrophenyl such as 'imidazole, 4-substituted imidazole,
- ester, 8-quinolyl thioester, or an ester with a N-hydroxy thioester, p-nitrophenyl thioester, p-cresyl thioester, ester, trichlorophenyl ester, pentachlorophenyl ester, carboxymethyl thioester, pyridyl ester, piperidinyl mesylphenyl ester, phenylazophenyl ester, phenyl 25
- (1H) pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, compound such as N,N-dimethylhydroxylamine, 1-hydroxy-2-1-hydroxybenzotriazole, 1-hydroxy-6-chlorobenzotriazole, etc:), and the like, 20
- Additionally, as a reactive derivative of the compound (1II), wherein A is aminomethylene, the compound 35

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of the following formula can also be used.

The suitable reactive derivative can optionally be selected from the above according to the kinds of the compounds (II) and (III) to be used practically.

(e.g. lithium, sodium, potassium, etc.), alkaline earth This reaction can be carried out in the presence of an organic or inorganic base such as alkali metal

alkali metal carbonate (e.g. sodium carbonate, potassium metal (e.g. calcium, etc.), alkali metal hydride (e.g. (e.g. calcium hydride, etc.), alkali metal hydroxide sodium hydride, etc.), alkaline earth metal hydride (e.g. sodium hydroxide, potassium hydroxide, etc.), 15

carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal triethylamine, etc.), pyridine compound (e.g. pyridine, lutidine, picoline, etc.), quinoline, and the like. potassium tert-butoxide, etc.), trialkylamine (e.g. alkoxide (e.g. sodium methoxide, sodium ethoxide, 2.5 20

of the free acid or a salt in this reaction, the reaction is preferably carried out in the presence of a condensing In case that the compound (III) is used in a form agent such as a carbodiimide compound [e.g. N,N'-

aminopropyl)carbodiimide, etc.]; a ketenimine compound N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethyldicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N*-(4-fiethylaminocyclohexyl) carbodiimide, N,N'-diethylcarbodiimide, (e.g. N,N'-carbonylbis(2-methylimidazole), 35 20

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benzotriazole derivative [e.g. 1-(4-chlorobenzenesulfonyloky)-6-chloro-lH-benrotriazole, etc.], a combination of pontamethyloneketene-M-cyclohoxylimine, diphenylketenetetrachloride, disulfide or diazenedicarboxylate (e.g. ether compounds (e.g. ethoxyacetylene, 8-chlorovinyl-N-cyclohexylimine, etc.); an olefinic or acetylenic rialkylphosphite or triphenylphosphine and carbon ethyl ether), a sulfonic acid ester of N-hydroxy-

pound (e.g. ethyl polyphosphate, isopropyl polyphosphate, thionyl chloride, oxalyl chloride, N-ethylbenzisoxazolium salt, N-ethyl-5-phenylisoxazolium-3-sulfonate, a reagent diethyl diazenedicarboxylate, etc.), a phosphorus com-(referred to as so-called "Vilsmeier reagent") formed phosphoryl chloride, phosphorus trichloride, etc.), by the reaction of an amide compound such as 12

N-methylformamide chloride, phosphoryl chloride, phosgene or the like. or the like with a halogen compound such as thionyl dimethylformamide,

The reaction is usually carried out in a conventional such as water, acetone, dioxane, acetonitrile, chloroform, solvent which does not adversely influence the reaction tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, Pyridine, hexamethylphosphoramide, etc., or a mixture benzene, methylene chloride, ethylene chloride, 20 2.5

Among these solvents, hydrophilic solvents may be used in a mixture with water.

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

(2) Process 2;

The compound (I-b) or a salt thereof can be prepared by subjecting the compound (I-a) or a salt thereof to removal reaction of the amino-protective group in $A^{\mathbf{1}}$.

Suitable method for this removal reaction may

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include conventional one such as hydrolysis, reduction and the like.

(i) For Hydrolysis:

Hydrolysis is preferably carried out in the presence of an acid.

hydrochloric acid, hydrobromic acid, sulfuric acid, etc.), trifluoroacetic acid, propionic acid, benzenesulfonic Suitable acid may be an inorganic acid (e.g. in organic acid (e.g. formic acid, acetic acid,

exchange resin and the like. In case that trifluoroacetic acid is used in this reaction, the reaction is preferably carried out in the presence of cation trapping agents acid, p-toluenesulfonic acid, etc.), an acidic ion-(e.g. anisole, etc.).

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The acid suitable for this hydrolysis can be selected removed, for example, this hydrolysis can preferably be according to the kinds of the protective group to be applied to the amino-protective group for A¹ such as substituted or unsubstituted lower alkoxycarbonyl, 20

ventional solvent which does not adversely influence The hydrolysis is usually carried out in a consubstituted or unsubstituted lower alkanoyl.

the reaction such as water, methanol, ethanol, propanol, The reaction temperature of this hydrolysis is not critical, and the reaction is usually carried out under mixture thereof, and further the above-mentioned acids can also be used as a solvent when they are in liquid. tetrahydrofuran, N,N-dimethylformamide, dioxane or a

cooling to at somewhat elevated temperature.

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction. Suitable reducing agents to be used in chemical (ii) For Reduction:

35 reduction are a combination of a metal (e.g. tin, zinc,

inon, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid,

colloidal platinum, platinum oxide, platinum wire, etc.), Suitable catalysts to be used in catalytic reduc-(e.g. platinum plate, spongy platinum, platinum black, tion are conventional ones such as platinum catalysts nydrochloric acid, hydrobromic acid, etc.).

Darium carbonate, etc.), nickel catalysts (e.g. reduced olack, palladium oxide, palladium on carbon, colloidal palladium catalysts (e.g. spongy palladium, palladium palladium, palladium on barium sulfate, palladium on catalysts (e.g. reduced cobalt, Raney cobalt, etc.), nickel, nickel oxide, Raney nickel, ett.), cobalt 20 2

iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like.

example, the chemical reduction can preferably be applied to the amino-protective group for Al such as halo(lower)alkoxycarbonyl and the like, and catalytic reduction can The reduction manner can be selected according to the kinds of the protective group to be removed, for preferably be applied to that such as substituted or 20

The reduction is usually carried out in a conventional solvent which does not adversely influence the unsubstituted ar(lower)alkoxycarbonyl, and the like. reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof.

Additionally, in case that the above-mentioned acids to also be used as a solvent. Further, a suitable solvent se used in chemical reduction are in liquid, they can to be used in catalytic reduction may be the above-30

mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a 35

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mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

The present invention includes, within the scope of the invention, cases that the protected amino group in transformed into free amino group and/or free carboxy R¹ and/or the protected carboxy group for R³ are group, respectively during the reaction.

Process 3:

the compound (1-d) or a salt thereof can be prepared by subjecting the compound (I.c) or a salt thereof to removal reaction of the amino-protective group in $R_{\rm a}^{\rm L}$.

This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like. 15

reaction conditions (e.g. reaction temperature, solvent, for the removal reaction of the amino-protective group etc.) are substantially the same as those illustrated The method of hydrolysis and reduction, and the

The present invention includes, within the scope of of the compound (I-a) in Process 2, and therefore are to be referred to said explanation. 20

the invention, cases that the protected amino group in A and/or the protected carboxy group(s) for \mathbb{R}^3 and A are transformed into free amino group and/or free carboxy group, respectively during the reaction. 52

(4) Process 4:

The compound (I-f) or a salt thereof can be prepared removal reaction of the carboxy-protective group for R_A³. by subjecting the compound (I-e) or a salt thereof to 30

This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like. The method of hydrolysis and reduction, and the 35

reaction conditions (e.g. reaction temperature, solvent, for the removal reaction of the amino-protective group etc.) are substantially the same as those illustrated of the compound (I-a) in Prucess 2, and therefore are to be referred to said explanation.

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of the invention, cases that the protected amino group(s) in \mathbb{R}^{\perp} and A and/or the protected carboxy group in A are The present invention includes, within the scope transformed into free amino group(s) and/or a free carboxy group, respectively during the reaction. 9

Process 5:

The Compound (1-e) or a salt thereof can be prepared by introducing a carboxy-protective group into the compound (I-f) or a salt thereof.

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The introducing agent of a carboxy-protective group to be used in this reaction may include a conventional esterifying agent such as an alcohol or its reactive

equivalent (e.g. halide, sulfonate, sulfate, diazo compound, etc.), and the like. 20

This reaction can also be carried out in the presence those given in the explanation of Process 1, and can preof a base, and suitable examples thereof are the same as ferably be carried out in the presence of metal iodide

This reaction is usually carried out in a conventional solvent which does not adversely influence the (e.g. sodium lodide, etc.).

reaction such as N,N-dimethylformamide, tetrahydrofuran, dioxane, methanol, ethanol, etc., or a mixture thereof. The reaction temperature is not critical, and the

reaction is usually carried out under cooling to at somewhat elevated temperature. 30

In case that the alcohol is used as the introducing be carried out in the presence of a condensing agent as agent of a carboxy-protective group, the reaction can

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Process 6: 3

The reduction can be carried out by a conventional pared by reducing the compound (I-g) or a salt thereof. method such as reduction using a reducing agent, cata-The compound (I-h) or a salt thereof can be prelytic reduction, and the like.

one used for conversion of a carbonyl group to a hydroxyborohydride (e.g. sodium borohydride, potassium borohyd-Suitable reducing agent may include a conventional methyl group such as metal borchydride, for example, alkali ride, sodium cyanoborohydride, etc.), lithium aluminum hydride, etc.; diborane; and the like.

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The catalyst to be used in the catalytic reduction may include the same ones as exemplified for the reduction in Process 2.

This reaction is usually carried out in a convenreaction such as water, methanol, ethanol, tetrahydrotional solvent which does not adversely influence the furan, dioxane; etc., or a mixture thereof.

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

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The compound (I-i) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the Process 7: compound (V).

include the same salts with a base for the compounds (I). This reaction is usually carried out in a conven-Suitable salts of the starting compound (IV) may tional solvent which does not adversely influence the reaction such as ethyl acetute, methylene chloride,

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chloroform, carbon tetrachloride, tetrahydrofuran, dioxane, water, etc., or a mixture thereof.

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

Process 8: 8

by subjecting the compound (I-k) or a salt thereof to removal The compound (I-2) or a salt thereof can be prepared reaction of the carboxy-protective group in $\mathtt{A}^\mathtt{b}$

This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like,

the removal reaction of the amino-protective group of the etc.) are substantially the same as those illustrated for reaction conditions (e.g. reaction temperature, solvent, compound (1-a) in Process 2, and therefore are to be The method of hydrolysis and reduction, and the reforred to said explanation.

formed into free amino group and/or free carboxy group, R^{\perp} and/or the protected carboxy group in R^3 are trans-The present invention includes, within the scope thereof, cases that the protected amino group in

respectively during the reaction.

(continued to the next page)

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thereof to removal reaction of the amino- and carboxyprepared by subjecting the compound (I-m) or a salt The compound (I-n) or a salt thereof can be protective groups in Rb. (9.) Process 9:

The method of hydrolysis and reduction, and the This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like.

reaction conditions (e.g. reaction temperature, solvent, the compound (1-a) in Process 2, and therefore are to etc.) are substantially the same as those illustrated for removal reaction of the amino-protective group of be referred to said explanation. 2

In this reaction, the amino- and carboxy-protective 15 groups can be removed separately or at a time.

(10) Process 10:

pared by subjecting the compound (I-o) or a salt thereof to removal reaction of the amino- and carboxy-protective The compound (I-p) or a salt thereof can be pre-

This reaction is carried out by a conventional groups in A⁸ 20

method such as hydrolysis, reduction, and the like.

25 reaction conditions (e.g. reaction temperature, solvent, for removal reaction of the amino-protective group of the compound (I-a) in Process 2, and therefore are to etc.) are substantially the same as those illustrated The method of hydrolysis and reduction, and the be referred to said explanation.

In this reaction, the amino- and carboxy-protective groups can be removed separately or at a time.

(11) Process 11:

The compound (1-k) or a salt thereof can be pre-35 pared by introducing a carboxy-protective group into

the compound (I-1) or a salt thereof.

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Process 5, and therefore, the reaction conditions (e.g. reaction temperature, solvent, etc.) are to be referred This reaction is carried out by substantially the carboxy-protective group into the compound (I-f) in same method as that illustrated for introducing the to said explanation.

(12) Process 12;

pared by reacting the compound (I-q) or a salt thereof The compound (I-r) or a salt thereof can be prewith the compound (VII).

This reaction is usually carried out in a convenreaction such as tetrahydrofuran, dioxane, water, etc., tional solvent which does not adversely influence the or a mixture thereof. 13

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature to under heating.

(13) Process 13:

The compound (I-s) or a salt thereof can be prepared by reacting the compound (1-r) or a salt thereof with a base.

Suitable base used in this Process may include the same ones as those exemplified in Process 1.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, etc., or a mixture thereof.

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reaction is usually carried out under cooling to warming. The object compounds (I) obtained according to the The reaction temperature is not critical, and the

purified in a conventional manner, for example, extraction, Processes 1 to 13 as explained above can be isolated and

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precipitation, fractional crystallization, recrystallization, chromatography, and the like.

and (XIV-c) are explained in detail in Processes A to F for the preparation of the starting compounds (ΙΙ-d), (ΙΙ-g), (ΙΙΙ-ḥ) το (ΙΙΙ-e), (ΙΙΙ-g), the following. (III-t), (IV)

Process A-1:

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The compound (II-b) or a salt thereof can be prepared by reacting the compound (II-a) or a salt thereof with the compound (VIII) or its reactive derivative at the mercapto

. Suitable salts of the compounds (II-a) and (II-b) may include the same salts with a base as exemplified for the compounds (I).

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Suitable "reactive derivative at the mercapto group"

of the compound (VIII) may include salts, with a base as exemplified for the compounds (I);

This reaction is preferably carried out in the pregiven in the explanation of Process 1. sence of a base and suitable examples thereof are the same as those

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such as N,N-dimethylformamide, dimethylsulfoxide, methanol, The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction ethanol, chloroform, etc., or a mixture thereof.

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reaction is usually carried out at ambient temperature The reaction temperature is not critical and the to under warming.

Process A-2: 2

pared by reducing the compound (II-b) or a salt thereof. The compound (II-c) or a salt thereof can be pre-

Suitable salts of the compound (II-c) may include the same salts with a base as exemplified for the compounds Ξ

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sulfinyl group to a thio group such as phosphorus halide The reducing agent to be used in this reaction may include a conventional one used for conversion of a

silicon halide (e.g. silicon tetrachloride, etc.); excess amount of acid halide such as lower alkanoyl halide (e.g. (e.g. phosphorus trichloride, phosphorus pentachloride, alkali metal halide (e.g. sodium iodide, etc.) and acid acetyl bromide, acetyl chloride, etc.); combination of etc.); stannous halide (e.g. stannous chloride, etc.); anhydride such as halo(lower)alkanoic anhydride (e.g.

The reaction is usually carried out in the presence of an acid scavenger such as lower alkene (e.g. 2-methyl 2-butene, etc.), lower alkylene oxide (e.g. ethylene trifluoroacetic anhydride, etc.); and the like.

The reaction is usually carried out in a conventional such as chloroform, methylene chloride, tetrahydrofuran, solvent which does not adversely influence the reaction oxide, propylene oxide, etc.) and the like. benzene, etc., or a mixture thereof.

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

Process A-3;

- The compound (II-d) or a salt thereof can be prepared by subjecting the compound (II-c) or a salt thereof to Suitable salts of the compound (11-d) may include removal reaction of the amino-protective group for Ra. the same ones as exemplified for the compounds (I). 52
- Suitable method for this removal reaction may include conventional one such as a combined method comprising iminohalogenation and iminoetherification, optionally followed by hydrolysis, and the like. 30

The first and second steps of this method are preferably carried out in an anhydrous solvent. Suitable solvent for the first step (i.e. iminohalogenation) is

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for the second step (i.e. iminostherification) is usually form, diethyl ether, tetrahydrofuran, dioxane, etc., and steps and the last step (i.e. hydrolysis step) are most an aprotic solvent such as mothylone chloride, chloro-These two These two the same as those in the above first step. steps are usually conducted under cooling. preferably conducted in one-batch system.

(e.g. phosphorus trichloride, phosphorus pentachloride, halogenating agent such as phosphorus halo compound phosphorus oxychloride, etc.), thionyl chloride, Suitable iminohalogenating agents include a phosphorus tribromide, phosphorus pentabromide, phosgene, and the like.

isopropanol, butanol, etc.) or the corresponding alkanol ethoxide, magnesium ethoxide, lithium methoxide, etc.), having alkoxy (e.g. 2-methoxyethanol, 2-ethoxyethanol, alkaline earth metal (e.g. sodium methoxide, potassium Suitable iminoetherifying agent may be an alcohol such as an alkanol (e.g. methanol, ethanol, propanol, etc.), and alkoxide of metal such as alkali metal, 20 2

Thus obtained reaction product is, if necessary, hydrolyzed in a conventional manner. and the like.

pouring the reaction mixture into water or a hydrophilic moistened or admixed with water, and if necessary, with addition of an acid or base as exemplified in Processes solvent such as alcohol (e.g. methanol, ethanol, etc.) The hydrolysis is preferably carried out at ambient temperature, or under couling, and proceeds simply 25

Process B-1:

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The compound (III-b) can be prepared by reacting the compound (III-a) with the compound (IX) or a salt thereof. 32

Suitabie sait of the compound (IX) may include This reaction is preferably carried out in the the sume one as exemplified for the compounds (1).

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This reaction is usually carried out in a conventional solvent which does not adversely influence the presence of a base as exemplified in Process 1.

reaction such as water, dioxane, tetrahydrofuran, etc., The reaction temperature is not critical and the or a mixture thereof.

10 reaction is usually carried out under cooling to warm-

Process B-2:

Suitable salts of the compound (III-c) may include The compound (III-c) or a salt thereof can be prethe same acid addition salt as exemplified for the pared by reducing the compound (III-b). compounds (1). 15

The reduction can be carried out by a conventional method such as chemical reduction, catalytic reduction, and the like.

temperature, solvent, etc.) are substantially the same reduction, and the reaction conditions (e.g. reaction as those illustrated for Process 2, and therefore are The method of chemical reduction and catalytic to be referred to said explanation.

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Process B-3;

ing an amino-protective group into the compound (III-c) The compound (III-d) can be prepared by introducor a salt thereof. 2

The introducing agent of an amino-protective group to be used in this reaction may include a conventional acylating agent such as the corresponding acid to the

acyl group as aforementioned or its reactive derivative 35

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tert-butoxycarbonyloxyimino-2-phenylacetonitrile, etc.), alkyl ketone substituted by lower alkoxycarbonyl (e.g. alkoxycarbonyloxyimino-2-phenylacetonitrile (e.g. 2-(e.g. acid halide, acid anhydride, etc.), 2-lower

lower alkyl acetoacetate, for example, methyl aceto-

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction acetate, etc., etc.), and the like.

such as water, methanol, ethanol, propanol, tetrahydro-This reaction is preferably carried out in the furan, dioxane, etc., or a mixture thereof.

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the same as those given in the explanation of Process 1.

presence of a base, and suitable examples thereof are

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

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The compound (III-e) or a salt thereof can be prepared by subjecting the compound (III-d) to removal reaction of the carboxy-protective group.

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the same salts with a base as exemplified for the $\operatorname{compounds}\left(\mathbf{I}\right)$. Suitable salts of the compound (III-e) may include

This reaction is carried out by a conventional method

reaction conditions (e.g. reaction temperature, solvent, for the removal reaction of the amino-protective group in Process 2, and therefore are to be referred to said etc.) are substantially the same as those illustrated explanation. Additionally, hydrolysis can be carried The method of hydrolysis and reduction, and the out in the presence of a base, and suitable examples thereof are the same as those in the explanation of such as hydrolysis, reduction, and the like. Process 1.

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35 Process B-5;

thereof to removal reaction of the carboxy-protective prepared by subjecting the compound (III-f) or a salt The compound (III-g) or a salt thereof can be group.

hose of the compound (III-g) may include the same salts Suitable salts of the compound (III-f) may include the same acid addition salts as exemplified above, and is exemplified for the compounds (I).

The reaction is substantially the same as Process B-4, and therefore, the reaction method, reaction conditions (e.g. reaction temperature, solvent, etc.) are to be referred to said explanation. ខ្ព

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The compound (III-e) or a salt thereof can be

prepared by introducing an amino-protective group into

This reaction is substantially the same as Process conditions (e.g. reaction temperature, solvent, etc.) B-3, and therefore, the reaction method and reaction the compound (III-g) or a salt thereof. re to be referred to said explanation.

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rocess C:

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The compound (IV) or a salt thereof can be prepared by reacting the compound (IV:a) or its reactive derivative at the amino group or a salt thercof with the compound (X) or its reactive derivative at the carboxy

the same ones as exemplified for the compounds (I), and Suitable salts of the compound (IV-a) may include chose of the compound (X) may include the same salts roup or a salt thereof.

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Process 1, and accordingly, the method, reaction condi-The reaction is substantially the same method as with a base as exemplified above.

tions (e.g. reaction temperature, solvent, base, etc.)

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are to be referred to said explanation.

In this process, carbonyl equivalents, for example,

alkylene having oxo, can also be used in this reaction and such acetal can easily be transformed into the oxo group by a conventional method (e.g. hydrolysis, etc.) acetal of the compound (X), wherein A^{S} is lower after the reaction.

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The compound (II-f) or a salt thereof can be prederivative at the carboxy group or a salt thereof with pared by reacting the compound (II-e) or a reactive

lower alkanol substituted by protected amino and protected carboxy groups (XII).

Suitable saits of the compounds (II-e) and (II-f) may include the same ones as exemplified for the compounds (I). Suitable reactive derivative at the carboxy group of the compound (II-e) may include the same ones as the compound (III) in Process 1, 10

This reaction is carried out by substantially the same method as that illustrated for introducing the

reaction temperature, solvent, etc.) are to be referred Process 5, and therefore, the reaction conditions (e.g. carboxy-protective group into the compound (I-f) in to said explanation.

Process D-2; 20

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pared by subjecting the compound (II-f) or a salt thereof to removal reaction of the amino-protective group for \mathbb{R}^a . The compound (II-g) or a salt thereof can be pre-

Suitable sait of the compound (II-g) may include the same ones as exemplified for the compounds (I).

same method as that illustrated for removal reaction of This reaction is carried out by substantially the the amino-protective group of the compound (II-c) in Process A-3, and therefore, the reaction conditions

e.g. reaction temperature, solvent, etc.) are to be eferred to said explanation.

rocess E-1:

The compound (111-1) can be prepared by reacting

the compound (III-h) with hydroxylamine or a salt thereof. 35

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The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as methanol, ethanol, etc., or a mixture thereof.

Process 1.

s

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

Process E-2:

active derivative at the carboxy group or a salt thereof. the compound (III-i) with the compound (XIII) or a re-The compound (III-j) can be prepared by reacting

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the same salt with a base as exemplified for the compounds Suitable salt of the compound (XIII) may include

Sultable reactive derivative at the carboxy group This reaction is carried out by substantially the of the compound (XIII) may include the same ones as illustrated for the compound (III) in Process 1. 20

same method as Process 1, and therefore, the reaction conditions (e.g. reaction temperature, solvent, etc.) are to be referred to said explanation.

Process E-3:

with ammonia.

pared by reacting the compound (III-j) or a salt thereof The compound (III-k) or a salt thereof can be pre-30

the same acid addition salt as exemplified for the com-Suitable salt of the compound (III-k) may include pounds (I). This reaction can be carried out in the absence of 35

or in the presence of a solvent which does not adversely reaction is usually carried out in the absence of a solinfluence the reaction such as dioxane, etc., and the

reaction is usually carried out under cooling to warming. geometrical isomers, it can be transformed into the other The reaction temperature is not critical and the In case that the compound (III-k) is one of the isomer in a conventional manner.

Process E-4;

to removal reaction of the carboxy-protective group for $\mathbb{R}^{\mathbf{c}}$. pared by subjecting the compound (III-k) or a salt thereof The compound (III-1) or a salt thereof can be pre-

Suitable salt of the compound (III-1) may include the This reaction is carried out by a conventional method same ones as exemplified for the compounds (I). such as hydrolysis, reduction, and the like. 15

etc.) are substantially the same as those illustrated for the removal reaction of the amino-protective group of the reaction conditions (e.g. reaction temperature, solvent, The method of hydrolysis and reduction, and the compound (I-a) in Process 2, and therefore are to be referred to said explanation. 20

Process F-1:

The compound (XIV-b) can be prepared by reacting the compound (XIV-a) or a reactive derivative at the hydroxy group with N-hydroxyphthalimide,

Suitable reactive derivative at the hydroxy group may include halide such as chloride, bromide, and the 30

This reaction is preferably carried out in the presence of a base as exemplified in Process 1.

In case that the compound (XIV-a) is used in a free

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presence of a condensing agent as exemplified in Process form, the reaction can usually be carried out in the

reaction such as tetrahydrofuran, N.N-dimethylformamide, This reaction is usually carried out in a conventional solvent which does not adversely influence the etc., or a mixture thereof.

reaction is usually carried out under cooling to warming. The reaction temperature is not critical and the

Process F-2:

The compound (XIV-c) or a salt thereof can be prepared by subjecting the compound (XIV-b) to removal reaction of the phthaloyl group.

the same acid addition salt as exemplified for the com-Suitable salt of the compound (XIV-c) may include pounds (I). ::

This reaction is carried out by a conventional method such as hydrolysis, and the like.

The method of hydrolysis, and the reaction conditions tially the same as those illustrated for removal reaction (e.g. reaction temperature, solvent, etc.) are substanof the amino-protective group of the compound (I-a) in Process 2, and therefore are to be referred to said explanation. 5 2 20

The starting compounds (II-d), (II-g), (III-b) to and (XIV-c) thus prepared can be isolated in a conventional manner as mentioned for the object compounds of the present invention. (III-e), (III-λ), (IV)

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treatment of the reaction mixture therein, in case that reactions in Processes 1 to 13 and A to F or the posttransformed into the other optical and/or geometrical and/or geometrical isomer(s), it may occasionally be the starting or object compounds possess an optical It is to be noted that, in the aforementioned

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isomer(s), and such cases are also included within the scope of the present invention.

position thereof, it may be transformed into its pharma-In case that the object compounds (I) have a free ceutically acceptable salts by a conventional method. carboxy group or free amino group at the 4th or 7th

novel and exhibit high antimicrobial activity, inhibiting The object compounds (I) and the pharmaceutically acceptable salts thereof of the present invention are

- the growth of a wide variety of pathogenic microorganisms including Gram-positive and Gram-negative microorganisms and are useful as antimicrobial agents, especially for oral administration. 10
- pounds (I), the test data on the in vitro antimicrobial Now in order to show the utility of the object comactivity of some representative compounds (I) of this invention are shown in the following. 15
- Cest: In vitro Antimicrobial Activity.

Test Compounds

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7-[2-(2-Aminothiazol-4-yl)-DL-glycolamido]-3methylthiomethyl-3-cephem-4-carboxylic acid (hereinafter referred to as Compound A) No. 1

- 7-[2-(3-Methanesulfonamidophenyl)-D-glycinamido}-3-methylthiomethyl-3-cephem-4-carboxylic acid trifluoroacetate (hereinafter referred to as Compound B)
- 7-[2-(3-Methanesulfonamidophenyl)-D-glycinamido]-3-allylthiomethyl-3-cephem-4-carboxylic acid trifluoroacetate (hereinafter referred to as Compound C) No. 3 20
- 7-[2-(3-Methanesulfonamidophenyl)-D-glycinamido]-3-methoxymethyl-3-cephem-4-carboxlic acid (hereinafter referred to as Compound D) No. 35

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Test Method

In vitro Antimicrobial activity was determined by the two-fold agar-plate dilution method as described below.

strain in Tripticase-soy broth (approximately 10⁸ viable agar) containing graded concentrations of antimicrobial was expressed in term of µg/ml after incubation at 37°C cells per ml) was streaked on heart infusion agar (HIagents, and the minimal inhibitory concentration (MIC) One loopful of an overnight culture of each test for 20 hours.

Test Results 1

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MIC (µg/ml)

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Microorganisms Test compounds	Staphylococcus aureus 209P.JC-1	Batilus subtilis ATCC 6633
Ą	1.56	0.78
æ	1.56	0.10
, 0	3.13	0.78
D	1.56	0.39

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the present invention are used in the form of conventional For therapeutic administration, the object compounds as active ingredients, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid (I) and the pharmaceutically acceptable salts thereof of pharmaceutical preparation which contains said compound, or liquid excipient which is suitable for oral, parenteral and external administr $\iota\iota$ tion. The

such as solution, suspension, syrup, emulsion, lemonade If needed, there may be included in the above preparapharmaceutical preparations may bu in solid form such as tablet, granule, powder, capsule, or liquid form and the like. 7.0

gents and other commonly used additives such as lactose, tions auxiliary substances, stabilizing agents, wetting talc, stearic acid, gelatin, agar, pectin, peanut oil, nagnesium stearate, terra alba, sucrose, corn starch, olive oil, cacao butter, ethyleneglycol and the like.

While the dosage of the compounds (I) may vary from and also depend upon the age, conditions of the parient, about 4,000 mg or even more per day may be administered 100 mg, 250 mg, 500 mg, 1000 mg, 2000 mg of the object a kind of diseases, a kind of the compounds (I) to be to a patient. An average single dose of about 50 mg, compounds (1) of the present invention may be used in applied, etc. In general, amounts between 1 mg and 20 25

treating diseases infected by pathogenic microorganisms. The following examples are given for the purpose of illustrating the present invention.

(continued to the next page)

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Preparation of the starting compounds Preparation .

3-chloromethyl-3-cephem-4-carboxylate-1-oxide (25 g) in To a solution of benzhydryl 7-(2-phenylacetamido)-N,N-dimethylformamide (150 ml) were added triethylamine (6.42 ml) and 2-propene-1-thiol (8.0 ml), and the mixture was stirred at 25°C for 3 hours.

and then dried to give benzhydryl 7-(2-phenylacetamido)aqueous solution of sodium chloride (1.5 1), followed by collecting the precipitated solid by filtration, which was washed with water and diisopropyl ether, The reaction mixture was poured into a saturated

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3-allylthiomethyl-3-cephem-4-carboxylate-1-oxide

dd, J.SHz, 8Hz), 4.8-5.6 (3H, m), 7.00 (6H, m), S.O (1H, d, J=5Hz), S.90 (1H, I.R. (Nujol): 1775, 1715, 1644, 1170, 1030 cm⁻¹ NMR 6ppm (DMSO-d₆): 3.00 (2H, d, J*7Hz), 3.6

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(1H, s), 7.4 (15H, s), 8.40 (1H, d, J*8Hz)

Benzhydryl 7-(2-phenylacetamido)-3-methylthiomethyl-3-cephem-4-carboxylate-1-oxide (13.7 g) was obtained by Preparation

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methanolic methanethiol (15 ml) in substantially the 5-cephem-4-carboxylate-1-oxide (15 g) with 30% same manner as that of Preparation 1.

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reacting benzhydryl 7-(2-phenylacetamido)-3-chloromethyl-

NAR Sppm (DMSO-d6): 1.80 (3H, s), 3.3-4.0 (6H, m), I.R. (Nujol): 3300, 1775, 1710, 1650, 1172, 1027 cm⁻¹

J=5Hz, 8Hz), 7.02 (1H, s), 7.50 (15H, s), 5.02 (1H, d, J=5Hz), 5.93 (1H, dd, 3.40 (1H, d, J-8Hz)

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Benzhydryl 7-(2-phenylacetamido)-3-ethylthiomethyl-

reparation

3-cephem-4-carboxylate-1-oxide (14.1 g) was obtained

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with ethanethiol (4.05 ml) in substantially the same chloromethyl-3-cephem-4-carboxylate-1-oxide (15 g) by reacting benzhydryl 7-(2-phenylacetamido)-3manner as that of Preparation 1.

(2H, q, J*7Hz), 3.5-4.0 (6H, m), 5.02 NMR &ppm (DMSO-d₆): 0.95 (5H, t, J=7Hz), 2.28 I.R. (Nujol): 3280, 1776, 1708, 1647, 1172, 1015 cm⁻¹

(1H, d, J-5Hz), 5.93 (1H, dd, J-5Hz, 8Hz), 7.02 (1H, s), 7.5 (15H, s), 8.43 (1H, d, J*8Hz)

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reparation 4

To a solution of benzhydryl 7-(2-phenylacetamido). stirring, and the stirring was continued for an hour. dropwise phosphorus trichloride (20 ml) at 5°C with 3-allylthiomethyl-3-cephem-4-carboxylate-1-oxide (26 g) in methylene chloride (500 ml) was added

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The mixture was poured into a mixture of methylene

pulverized with diisopropyl ether to give benzhydryl (200 ml) and dried over anhydrous magnesium sulfare. 7-(2-phenylacetamido)-3-allylthiomethyl-3-cephem-4separating out the organic layer, which was washed chloride (200 ml) and water (400 ml), followed by twice with an aqueous solution of sodium chloride After removal of the solvent, the residue was carboxylate (22 g).

NMR (DMSO-d₆): 3.0 (2H, d J*7Hz), 3.6 (6H, m), (1H, s), 7.40 (1SH, m), 9.10 (1H, d, 5.00 (1H, d, J=Silz), 5.67 (1H, dd, J=5Hz, 8Hz), 4.8-5.5 (3H, m), 6.90 I.R. (Nujo1): 1770, 1715, 1650 cm-1 J-8Hz)

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To a solution of benzhydryl 7-(2-phenylacetamido)-Preparation 5

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3-methylthiomethyl.3-cephem-4-carboxylate-1-oxide

2-methyl-2-butene (5.7 ml), followed by adding dropwise acetyl bromide (5.2 ml) under ice-cooling and stirring over anhydrous magnesium sulfate and then evaporated with an aqueous solution of sodium chloride, dried mixture was adjusted to pH about 5 with an aqueous solution of sodium bicarbonate, washed three times (15.1 g) in methylene chloride (150 ml) was added for half an hour. After addition of water, the under reduced pressure to give benzhydryl 7-[2phenylacetamido) - 3-methylthiomethyl - 3-cephem-4carboxylate (13.5 g).

(1H, d, J-SHz), 5.75 (1H, dd, J-SHz, broad s), 3.66 (2H, broad s), 5.23 NMR $\rm fppm~(DMSO-d_6):~1.83~(3H,~s),~3.60~(4H,$ 8Hz), 6.97 (1H, s); 7.43 (15H, s), I.R. (Nujol): 3380, 1785, 1715, 1652 cm⁻¹ 9.17 (1H, d, J-8Hz)

Benzhydryl 7-(2-phenylacetamido)-3-ethylthiomethyl-3-cephem-4-carboxylate (23 g) was obtained by reacting bromide (10.2 ml) in the presence of 2-methy1-2-butene (11.1 ml) in substantially the same manner as that of benzhydryl 7-(2-phenylacetamido)-3-ethylthiomethyl-3cephem-4-carboxylate-1-oxide (30 g) with acetyl Preparation 5.

ММR бррm (DMSO-d₆): 1.00 (3H, т, J-7Hz), 2.33 (2H, q, J-7Hz), 3.56 (6H, broad s), 5.17 (1H, d, J*SHz), 5.76 (1H, dd, I.R. (Nujol): 3300, 1772, 1701, 1650 cm⁻¹ J-SHz, 8Hz), 7.00 (1H, s), 9.13 (1H, d, J=8Hz)

Preparation 7

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(100 ml) were added benzhydryl 7-(2-phenylacetamido)-(16.1 g) and pyridine (6.3 ml) in methylene chloride To a suspension of phosphorus pentachloride

bicarbonate until the pH value of the aqueous solution inhydrous magnesium sulfate and evaporated to dryness. ether to give benzhydryl 7-amino-3-allylthiomethyl-3eparating out the organic layer, it was washed with The residue obtained was pulverized with diisopropyl To the separated methylene 3-allylthiomethyl-3-cephem-4-carboxylate (22 g) and nethylene chloride (100 ml) at 5°C, and the mixture To this mixture was added water (10 ml) and thereto, followed by stirring at -10°C for half an in aqueous solution of sodium chloride, dried over After cooling to -20°C,methanol (10 ml) was added chloride was added an aqueous solution of sodium vas stirred at the same temperature for an hour. occame 5.0, and the mixture was shaken. After stirred for 10 minutes.

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d, J=5Hz), 4.5-5.6 (3H, m), 6.91 (1H, s), NMR dppm (DMSO-d6): 2.93 (2H, d, J*7Hz), 3.3-3.7 (4H, m), 5.00 (1H, d, J-SHz), 5.60 (1H, I.R. (Nujol): 1770, 1710 cm-1 7.5 (10H, m)

cephem-4-carboxylate (6.5 g).

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carboxylate (5.0 g) was obtained by reacting benzhydryl substantially the same manner as that of Preparation 7. Benzhydryl 7-amino-3-methylthiomethyl-3-cephem-4-7. (2-phenylacetamido)-3-methylthiomethyl-3-cephem-4carboxylate (13.5 g) with phosphorus pentachloride (7.74 g), pyridine (3 ml) and methanol (100 ml) in I.R. (Nujol): 1765, 1725 cm⁻¹

broad s), 3.60 (ZH, broad s), 4.83,5.13 (2H, ABq, J=5Hz), 6.97 (1H, s), 7.40 NMR oppm (DMSO-d₆): 1.81 (3H, s), 3.52 (2H,

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Preparation 9

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Benzhydryl ?-amino-3-ethylthiomethyl-3-cephem-4-

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benzhydryl 7-(2-phenylacetamido)-3-ethylthiomethyl-3methanol (165 ml) in substantially the same manner pentachloride (12.90 g), pyridine (5.0 ml) and carboxylate (10.0 g) was obtained by reacting cephem-4-carboxylate (23.0 g) with phosphorus as that of Preparation 7.

ABq, J=5Hz), 7.00 (1H, s), 7.43 (10H, s) NMR 6ppm (DMSO-d₆): 0.96 (3H, t, J=7Hz), 2.30 (2H, q, J=7Hz), 3.50 (2H, broad s), 3.60 (2H, broad s), 4.80,5.17 (2H, I.R. (Nujol): 1770, 1720 cm⁻¹

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bromine (1.24 g) in methylene chloride (10 ml) at -30°C To a solution of diketene (1.3 ml) in methylene chloride (10 ml) was added dropwise a solution of

with stirring, and the stirring was continued at -20°C with stirring, and the stirring was continued at -10°C trimethylsilylocetamide (5.46 g) in methylene chloride for half an hour. After addition of water, the resulsolution of sodium bicarbonate, followed by separating out the organic layer, which was washed with water and dryness to give benzhydryl 7-(4-bromoacetoacetamido)--bromoacetoacetyl bromide. This solution was added nethylthiomethyl-3-cephem-4-carboxylate (4.44 g) and (100 ml) at -30 to -20°C over a period of 5 minutes tant mixture was adjusted to pll 7.5 with an aqueous anhydrous magnesium sulfate, and then evaporated to an aqueous solution of sodium chloride, dried over dropwise to a solution of benzhydryl 7-amino-3or half an hour to prepare a solution of

5.73 (111, dd, J=4Hz, 8Hz), 6.86 (111, s), NMR &ppm (DMSO-d6) : 1.77 (3H, s), 3.6 (6H, m), 3-methylthiomethyl-3-cephem-4-carboxylate (6.0 g). 4.33 (2H, s), 5.15 (1H, d, J=4Hz), IR (Nujol) : 1770, 1710, 1625 cm-1

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7.3 (10H, m), 9.1 (1H, d, J=8Hz) reparation 11

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To a solution of ethyl 2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetic acid (syn isomer)(19 g) in methanol (200 ml) were added 50% formic acid (200 ml) and zinc adjusted to pH 6.5 with 4N aqueous solution of sodium 5 hours. After filtration, the reaction mixture was hydroxide, followed by addition of ethanol (150 ml), (29 g), and the mixture was stirred at 5 to 10°C for мater (150 ml). The resultant aqueous solution маs evaporated, followed by dissolving the residue in

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reparation 12

acetate at 45°C, and the reaction mixture was stirred over magnesium sulfate. The solution was evaporated equivalent volume of diphenyl diazomethane in ethyl vas washed with 5% aqueous sodium bicarbonate and a at the same temperature for an hour. The solution saturated aqueous sodium chloride, and then dried Bromoacetic acid (10.45 g) was dissolved in To the solution was added an methanol (30 ml).

mixture was filtered, followed by removal of the organic

(18.2 g) and triethylamine (8.0 g): After stirring 2-tert-butoxycarbonyloxyimino-2-phenylacetonitrile at ambient temperature for 24 hours, the reaction solvent. The remained aqueous solution was washed with

acid and then extracted with ethyl acetate. The extract

was washed with an aqueous solution of sodium chloride, ethyl acetate, adjusted to pH 4 with 10% hydrochloric

dried over anhydrous magnesium sulfate and evaporated

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reduced pressure to give benzhydr/l 2-phthalimidooxyacetate dried over magnesium sulfate, and then evaporated under dissolved in methylene chloride (700 ml). The solution riethylamine (15,1 ml), and the reaction mixture was resultant mixture was poured into a saturated aqueous sodium chloride (500 ml). The precipitates were colsolution was added N-hydroxyphthallmide (11.7 g) and was washed with a saturated aqueous sodium chloride, in vacuo to give an oily product. This oil was dislected by filtration, washed with water, and then To the stirred at amblent temperature for an hour. The solved in N,N-dimethylformamide (60 ml).

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butoxycarbonyl-2-(2-formamidothiarol-4-y1)glycine (3.3 g).

WHR 6ppm (DMSO-46) : 1.40 (9H, s), 5.18 (1H, d,

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1540, 1510 cm⁻¹

J-8Hz), 7.17 (1H, s), 8.43 (1H, s)

which was washed with diethyl ether to obtain N-tert-IR (Nujol) : 3250, 3180, 1720, 1700, 1670, 1640,

to dryness under reduced pressure to give a residue,

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IR (Nujol) : 1754, 1730 cm-1 (20.4 g), mp 173-175°C,

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(continued to the next page)

NNR &ppm (CDC13,6):4.93 (ZH,S),7.0 (1H,S), 7.3 (10H,S), 7.73 (4H, s). To a solution of benzhydryl 2-phthalimidooxy-Preparation 13

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were collected by filtration and washed with methylene at ambient temperature for an hour. The precipitates methanol (7 ml). The reaction mixture was stirred chloride. The filtrate and the washings were comacetate (10 g) in methylene chloride (100 ml) was added a solution of hydrazine hydrate (6.08 g) in bined, adjusted to pH 7.0 with conc. hydrochloric acid, and washed with a saturated aqueous sodium chloride, and then dried over magnesium sulfate. 35 30

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The solution was evaporated in vacuo to give benzhydryl 2-aminooxyacetate (6.0 g). IR (film): 3320, 1750 cm

(2H, broad s), 7.00 (1H, s), 7.3 (10H,s) . NMR 6ppm (CDC13, 6): 4.33 (2H, s), 5.86

Preparation 14

(6 ml) was added a solution of benzhydryl 2-aminooxyglyoxylic acid (6.0 g) in water (60 ml) and pyridine To a suspension of (2-formamidothiazol-4-yl)acetate (9.0 g) in tetrahydrofuran (40 ml),

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a saturated aqueous sodium bicarbonate and a saturated squeous sodium chloride, and then dried over magnesium added ethyl acetate (200 ml). The separated organic layer was washed with 5% hydrochloric acid (100 ml), The reaction mixture was stirred at ambient temperature for 3 hours. To the resultant solution was

formamidothiazol-4-yl)-2-benzhydryloxycarbonylmethoxyiminoacetic acid (syn isomer) (13.0 g), mp 143-151*C.
1R (Nujol) : 3150, 1733, 1692 cm⁻¹

sulfate. The solvent was distilled off to give 2-(2-

(1H, s), 7.40 (20H, m), 7.56 (1H, s), NMR 6ppm (DNSO-d6) : 5.0 (2H, broad s), 6.97 8.60 (1H, s), 12.77 (1H, broad s)

To a solution of 2-benzhydryloxy.carbonylmethoxy-Preparation 15 52

minutes. To the reaction mixture was added triethylamine bicarbonate. The aqueous layer was adjusted to pH 2.0 added ethyl acetate (100 ml) and water (100 ml), and Isomer) (7.5 g) in tetrahydrofuran (40 ml) was added (5.3 ml) at -10°C, and then the mixture was stirred for 90 min at 0 to 5°C. To the above mixture were adjusted to pil 7.5 with a saturated aqueous sodium .mino-2-(2-formamidothlazol-4-yl)acetic acid (syn trifluoroacetic anhydride (7.9 g) at -16°C for 10

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with conc. hydrochloric acid and extracted with

ethyl acetate (200 mi). The organic layer was washed over magnesium sulfate. The solvent was removed by with a saturated aqueous sodium chloride and dried

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substance was collected by filtration to give crystalline 2-benzhydryloxycarbonylmethoxyimino-2-[2-(2,2,2n-Hexane was added to the oil and the precipitated evaporation under reduced pressure to give an oil. trifluoroacetamido)thiazol-1-yl]acetic acid (syn (somer) (6.0 g), mp 178-180°C.

NMR &ppm (DMSO-d6) : 4.98 (2H, s), 6.92 (1H, s), 7.32 (10H, m), 7.69 (1H, s) 1R (Nujo1) : 1752, 1726 cm-1

(continued to the next page)

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Precaration of the object compounds

To a solution of N-tert-butoxycarbonyl-2-(3-

followed by extracting with methylene chloride (100 ml). to a solution of benzhydryl 7-amino-3-methylthiomethylglycinamido]-3-methylthiomethyl-3-cephem-4-carboxylate the activated acid. This solution was added dropwise The extract was washed twice with 5% aqueous solution of sodium bicarbonate (50 ml) and an aqueous solution same temperature for 40 minutes to give a solution of 3-cephem-4-carboxylate (3.0 g) in methylene chloride stirring, and the stirring was continued at the same vas added dropwise a solution of ethyl chloroformate with stirring, and the stirring was continued at the temperature for an hour. After addition of water, (0.91 ml) in tetrahydrofuran (10 ml) at -10 to -7°C the reaction mixture was stirred for half an hour, 100 ml) at -30°C over a period of 5 minutes with triethylamine (1.34 ml) in tetrahydrofuran (50 ml) of sodium chloride, and then dried over anhydrous magnesium sulfate, followed by evaporation under outoxycarbonyl-2-(3-methanesulfonamidophenyl)-Dmethanesulfonamidophenyl).D-glycine (3.3 g) and reduced pressure to give benzhydryl 7-[N-tert-

NHR $\rm \delta\,ppm$ (DMSO- $\rm d_6)$: 1.36 (9H, s), 1.76 (3H, s), 8Hz), 6.93 (1H, s), 7.1-7.4 (14H, m), (1H, d, J=SIIz), 5.73 (1H, dd, J=SHz, 2.98 (3H, s), 3.5-3.8 (4H, m), 5.12 I.R. (Nujol): 1780, 1710, 1680, 1152 cm⁻¹ 9.93 (1H, d, Ja8Hz)

Example 2

N-tert-butoxy carbonyl-2-(3-methanesulfonamidophenyl).Dethylthiomethyl-3-cephem-4-carboxylate (3.08 g) with glycine (5.3 g) in substantially the same manner as ethylthiomethyl-3-cephem-4-carboxylate (5.4 g) was Benzhydryl 7-[N-tert-butoxycarbonyl-2-(5methanesulfonsmidophenyl)-D-glycinamido]-3obtained by reacting benzhydryl 7-amino-3that of Example 1.

NMR dppm (DMSO-d₆): 0.98 (3H, t, J*7Hz), 1.38 I.R. (Nujol): 3250, 1780, 1700, 1530, 1490, 1455 cm⁻¹

(3H, s), 3.4-3.8 (4H, m), 5.12 (1H, d, (14H, m), 9.89 (1H, d, J*8Hz), 10.43 J=5Hz), 5.24 (1H, m), 5.73 (1H, dd, (9H, s), 2.28 (2H, q, Ja7Hz), 2.97 J=SHz, 7Hz), 6.93 (1H, s), 7.0-7.7

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Example 3

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NMR dppm (DMSO-d₆): 1.5 (9H, s), 2.3 (2H, broad s), solution was extracted with methylene chloride (50 ml). 3.24 (3H, s), 3.51 (2H, s), 4.15 (2H, s), To a suspension of tert-butyl 7-amino-3-methoxysolution of sodium bicarbonate. After separating out over anhydrous magnesium sulfate and then treated with methylene chloride (200 ml) was added water (100 ml), an activated charcoal, followed by evaporation under followed by adjusting to pH about 6 with an aqueous the methylene chloride layer, the remaining aqueous The combined methylene chloride solution was washed methyl-3-cephem-4-carboxylate tosylate (13.1 g) in With an aqueous solution of sodium chloride, dried reduced pressure to give tert-butyl 7-amino-3-I.R. (Nujol): 3370, 1760, 1740, 1710 cm-1 methoxymethyl-3-cephem-4-carboxylate (5.7 g).

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4.8 (1H, d, J.SHz); S.04 (1H, d, J-SHz) tetrahydrofuran (95 ml) was added dropwise a solution of ethyl chloroformate (2.8 g) in dry tetrahydrofuran with stirring, and stirring was continued at the same temperature for 40 minutes to prepare a solution of (25 ml) at -10 to -7°C over a period of 10 minutes glycine (8.89 g) and triethylamine (2.61 g) in dry On the other hand, to a solution of N-tertbutoxycarbonyl-2-(3-methanesulfonamidophenyl)-Dthe activated acid.

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7-[N-tert-butoxycarbony1-2-(3-methanesulfonamidophenyl)aqueous solution was extracted with methylene chloride. After addition of water (100 ml), the reaction mixture was stirred for half an hour. The methylene chloride To a solution of the compound (5.65 g) obtained D-glycinamido]-3-methoxymethyl-3-cephem-4-carboxylate according to Example 3-(1) in dry methylene chloride activated acid prepared above at -30°C over a period evaporation under reduced pressure to give tert-butyl layer was separated out therefrom and the remaining twice with 5% aqueous solution of sodium bicarbonate (100 ml) and an aqueous solution of sodium chloride, The combined methylene chloride solution was washed of 10 minutes with stirring, and the stirring was dried over anhydrous magnesium sulfate, and then (190 ml) was added dropwise the solution of the treated with an activated charcoal, followed by Continued at the same temperature for an hour.

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NMR &ppm (DMSO-d₆): 1.36 (9H, s), 1.46 (9H, s), 2.97 (3H, s), 3.18 (3H, s), 3.4 (2H, 5.73 (1H, dd, J-SHr, 8Hz), 6.93-7.43 (1H, d, J=SHz), 5.24 (1H, d, J=8Hz), broad s), 4.07 (2H, broad s), 5.03 I.R. (Nujol): 3250, 1780, 1710, 1680 cm-1

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(4H, m), 7.5 (1H, d, J-8Hz), 9.16

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(1H, d, J.8Hz), 9.73 (1H, broad s), The compounds described in the following Examples methanesulfonamidophenyl)-D-glycine in substantially 4 to 7 were obtained by reacting the corresponding 7-aminocephalosporanic acid derivative with 2-(3the same manner as that of Example 3,

7-[2-(3-Methanesulfonamidophenyl)-D-glycinamido]. I.R. (Nujol): 1758, 1687 (shoulder), 1666, 1144, 3-methylthiomethyl-5-cephem-4-carboxylic acid.

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974 cm⁻¹

7-[2-(3-Methanesulfonamidophenyl)-D-glycinamido]-3-ethylthiomethyl-3-cephem-4-carboxylic acid.

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I.R. (Nujol): 3500, 3150, 1780, 1685, 1460 cm-1 Example 6

7-[2-(3-Methanesulfonamidophenyl)-D-glycinamido]-I.R. (Nujol): 3500, 3150, 1760, 1685 cm-1 3-methoxymethyl-3-cephem-4-carboxylic acid. Example 7

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7-[2-(3-Methanesulfonamidophenyl)-D-glycinamido]. 3-allylthiomethyl-3-cephem-4-carboxylic acid tri. fluoroacetate.

I.R. (Nujol): 1760, 1680, 1600, 1140 cm⁻¹ Example 8

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ether (300 ml), and the precipitated solid was collected A mixture of benzhydryl 7-[N-tert-butoxycarbonylthe reaction mixture was added dropwise to dissopropyl by filtratión, washed with diisopropyl ether and then stirred at 25°C for 15 minutes. After the reaction, anisole (5.0 ml) in trifluoroacetic acid (20 ml) was dissolved in a mixture of water (50 ml) and ethyl 2.(3-methanesulfonamidophenyl)-D-glycinamido]-3methylthiomethyl.3-cephem-4-carboxylate (6.5 g), acetate (50 ml). After the aqueous layer was

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and the fractions containing the desired compound were followed by removal of ethyl acetate from the aqueous The resultant aqueous solution was adjusted to pH 3,8 After washing with water (180 ml), elution was carried out with 30% isopropyl alcohol, with an aqueous solution of sodium bicarbonate and separated out, it was washed with ethyl acetate, subjected to column chromatography using "Diaion solution completely under reduced pressure. HP-20" (90 ml).

(continued to the next page)

I.R. (Nujol): 1758, 1687 (shoulder), 1666, 1144, methylthiomethyl-3-cephem-4-carboxylic acid (4.8 g). methanesulfonamidophenyl) -D-glycinamido]-3collected and lyophilized to give 7-[2-(3-

NMR &ppm (D,0 + DCl): 1.98 (5H, s), 3.15 (3H, s), 3.45 (2H, broad s), 3.56 (2H, broad s), 5.12 (1H, d, J=5Hz), 5.30 (1H, s), 974 cm⁻¹

5.70 (1H, d, JuSHz), 7.45 (4H, s) Example 9

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7-[2-(3-Methanesulfonamidophenyl).D-glycinamido]. presence of anisole (7.4 ml) in substantially the same glycinamido]-3-ethylthiomethyl-3-cephem-4-carboxylate 3-ethylthiomethyl -3-cephem-4-carboxylic acid (1.6 g) (3.7 g) with trifluoroacetic acid (7.4 ml) in the butoxycarbonyl-2-(3-methanesulfonamidophenyl)-Dwas obtained by reacting benzhydryl 7-[N-tertmanner as that of Example 8, mp 188°C (dec.).

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I.R. (Nujol): 3500, 3150, 1780, 1685, 1460 cm-1 NMR 6ppm (D,O + DCl): 1.13 (3H, t, J=7Hz), 2.48 (2H, q, J-7Hz), 5.11 (3H, s), 3.3-3.8 (4H, m), 5.30 (1H, s), 5.65 (1H, d, J=SHz), 7.43 (4H, s)

The reaction mixture was poured into dissopropyl ether (750 ml), followed by stirring at ambient temperature period of 10 minutes with stirring, and the stirring glycinamido]-3-methoxymethyl-3-cephem-4-carboxylate for 20 minutes. After the precipitated solid was trifluoroacetic acid (33.75 ml) below 15°C over a butoxycarbonyl-2-(3-methanesulfonamidophenyl)-D-(15 g) in anisole (11.25 ml) was added dropwise was continued at 15 to 20°C fo; half an hour. To a solution of tert-butyl 7-(N-tert-Example 10

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collected by filtration and washed with diisopropyl

22.23

The combined aqueous solution was concentrated adjusted to pH about 3.8 with ar aqueous solution of sodium bicarbonate, followed by subjecting to column "Diaion HP-20" (225 ml), which was washed with water collected and evaporated under reduced pressure, and other, it was poured into a mixture of ethyl acetate (450 ml) and then eluted with 30% isopropyl alcohol. (100 ml) and water (100 ml) and stirred for a while. The fractions containing the desired compound were chromatography using non-ionic adsorption resin . and the remaining organic layer was extracted with The aqueous solution was separated out therefrom, under reduced pressure, and the concentrate was

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NMR 6ppm (D, 0 + DC1): 3.13 (3H, s), 3.26 (3H, s), 5.06 (1H, d, J=SHz); 5.27 (1H, s), 5.73 nethoxymethyl-3-cephem-4-carboxylic acid (4.45 g). 3.42 (2H, q, J-18Hz), 4.25 (2H, s), I.R. (Nujol): 3500, 3150, 1760, 1685 cm^{-l} [1H, d, J#SHz], 7.42 (4H, s)

Example 11

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hour, followed by adding dropwise to dissopropyl ether. weshed with diisopropyl ether and then dissolved in a Benzhydryl 7-amino-3-allylthiomethyl-3-cephem-4-The aqueous layer was separated out and washed with and anisole (15 ml) was stirred at 20°C for half an carboxylate (3.3 g) and N-tert-butoxycarbonyl-2-(3treated in substantially the same manner at that of The presipitated solid was collected by filtration, mixture of water (50 ml) and ethyl acetate (50 ml). A mixture of this oil, trifluoroacetic acid (15 ml) methanesulfonamidophenyl)-D-glycine (3:44 g) were diethyl ether, followed by removal of the organic example 1 to give an oily product (6.5 g).

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The resultant aqueous methanesulfonemidophenyl)-D-glycinemido]-3-111ylthiomethyl-3-cephem-4-carboxylic acid solution was lyophilized to give 7-[2-(3solvent therefrom completely. rifluoroacetate (2 g).

WAR &ppm (D20 + DC1): 3.20 (2H, m), 3.23 (3H, s), 3.6 (7H, m), 5.2 (1H, d, J=SHz), 5.45 (1H, s), 5.80 (1H, d, J.SHz), 7.55 I.R. (Nujol): 1760, 1680, 1600, 1140 cm⁻¹

Example 12

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the residue was lyophilized to give 7-[2-(3methanesulfonamidophenyl).D-glycinamido].3.

To a solution of benzhydryl 7-[4-bromoacetoacetamido]washed twice with an aqueous solution of sodium chloride, 30°C for an hour. The reaction mixture was poured into a mixture of ethyl acetate (100 ml) and water (100 ml), followed by separating out the organic layer, which was with stirring, and the stirring was continued at 28 to dried over anhydrous magnesium sulfate and then evapocetrahydrofuran (30 ml) was added dropwise a solution 3-methylthiomethyl-3-cephem-4-carboxylate (6.0 g) in in tetrahydrofuran (30 ml) and water (24 ml) at 25°C of thiourea (0.85 g) and sodium bicarbonate (0.94 g) acetamido]-3-methylthiomethyl-5-cephem-4-carboxylate rated to give benzhydryl 7-[2-(2-aminothiazol-4-yl)-

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NMR 6ppm (DMSO-d₆) : 1.85 (3H, s), 3.3-3.8 (6H, m), J=5Hz, 8Hz), 6.32 (1H, s), 7.00 (1H, s), 5.25 (1H, d, J=5Hz), 5.80 (1H, dd, 7.43 (10H, s), 8.95 (1H, d, J.8811z) IR (Nujol) : 1773, 1715, 1653 cm-1

xample 13

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carboxylate tosylate (2.0 g) was dissolved in a mixture of acetone (40 ml) and a saturated aqueous solution of tert.Eutyl 7-amino-3-methoxymethyl-3-cephem-4sodium bicarbonate (15 ml), and thereto was added

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phosphorus oxychloride (0.85 g) and N,N-dimethylformamide 7.[2.(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]dryness under reduced pressure to give a residue, which (0.41 g) in tetrahydrofuran (10 ml), at 0 to 5° C over a was triturated with diethyl ether to obtain tert-butyl value of the reaction mixture was maintained at $pH\ 7.0$ extract was washed with 5% aqueous solution of sodium carbonate. After stirring for an hour, the reaction bicarbonate and water, dried and then evaporated to 3-methoxymethyl-3-cephem-4-carboxylate (syn isomer) extracting twice with ethyl acetate. The combined dropwise a solution of the activated acid, which was period of 10 minutes. During the addition, the PH mixture was diluted with water (50 ml), followed by to 7.5 with a saturated aqueous solution of sodium prepared from 2-(2-formamidothiazol-4-yl)-2methoxyiminoacetic acid (syn isomer)(1.06 g),

NMR $\rm dypm~(DMSO-d_6)$: 1.49 (9H, s), 3.21 (3H, s), IR (Nujol) : 3250, 3100, 1790, 1710, 1660 cm⁻¹ 3.28 (2H, broad s), 3.89 (3H, s), 4.1 (1H, dd, J=SHz, 8Hz), 7.36 (1H, s), r2H, s), S.16 (1H, d, JaSHz), S.80 8.48 (1H, s), 9.6 (1H, d, J=8Hz), 12.66 (1H, broad s)

Example 14

methoxyiminoscetamido]-3-methylthiomethyl-3-cephem-4thiazol-4-yl)-2-methoxyiminoacetic acid (syn isomer) (0.85 g) according to the similar manner to that of cephem-4-carboxylate (0.90 g) with 2-(2-formamidoreacting tert-buryl 7-amino-3-methylthiomethyl-3tert-Butyl 7-[2-(2-formamidorhiazol-4-yl)-2carboxylate (syn isomer)(0.91 g) was obtained by Example 13.

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3.29 (2H, broad s), 3.55 (2H, ABq, J-13Hz), WMR 6ppm (DMSO-d₆) : 1.47 (911, s), 1.97 (3H, s), 3.87 (5H, s), 5.21 (1H, d, J=SHz), 5.76 (1H, dd, J*5Hz, 8Hz), 7.38 (1H, s), 8.49 (1H, s), 9.66 (1H, d, J-8Hz), IR (Nujo1): 3250, 3050, 1780, 1690 cm⁻¹ 12.56 (1H, broad s)

15 to 17 were obtained by reacting the 7-aminocephalos-The compounds described in the following Examples according to the similar manner to that of Example 13, ooranic acid derivatives with the corresponding, acid

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7-[2-(2-Aminothiazol-4-yl)acetamido]-3methylthiomethyl-3-cephem-4-carboxylic acid IR (Nujol) : 1763, 1654 cm-1

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7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]--methoxymethyl-3-cephem-4-carboxylic acid hydrochloride

IR (Nujol) : 3300, 1780, 1720, 1660, 1640 cm⁻¹ (syn isomer)

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3-methylthiomethyl-3-cephem-4-carboxylic acid (syn isomer) 7-[2-(2-Aminothiazol-4-y1)-2-methoxyiminoacetamido]-IR (Nujol) : 5350, 1770, 1670 cm⁻¹ Example 17

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(3.3 g), trifluoroacetic acid (10 ml) and anisole (10 ml) vl)acetamido].3-methylthiomethyl-3-cephem-4-carboxylate The remained aqueous solution was poured into a mixture of ethyl acetate (100 ml) and water (100 ml), followed n methylene chloride (10 ml) was stirred at 10°C for n hour. After benzene (50 ml) was added to the reac-The mixture of benzhydryl 7-[2-(2-aminothiazol-4tion mixture, the trifluoroacetic acid therein was azeotropically removed under reduced pressure.

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separating out the aqueous solution, the organic solvent by adjusting to pH 7.5 with sodium bicarbonate. After reduced pressure, followed by adjusting to pH 3.0 with vas removed therefrom by evaporation completely under (2-aminothiarol-4-yl)acetamido]-3-methylthiomethyl-3collected by filtration and then dried to give 7-[2-104 hydrochloric acid. The precipitated solid was

cephem-4-carboxylic acid (0.95 g). IR (Nujol) : 1763, 1654 cm 1

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5.67 (1H, dd, J*5Hz, 8Hz), 6.38 (1H, s), 3.65 (4H, broad s), 5.17 (1H, d, J=5Hz), $\label{eq:MMR_sppm} \text{MMR Sppm (DMSO-d_6)} : 2.01 (3H, s), 3.48 (2H, s),$ 9.00 (1H, d, J*8Hz)

Example 19

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in methylene chloride (20 ml) were added trifluoroacetic for 3 hours. After evaporation of the reaction mixture, sodium bacarbonate. The resultant aqueous solution was acid (4.4 g) and anisole (0.2 ml), and the mixture was gradually warmed at 40°C, followed by stirring at 10°C 30 minutes in diethyl ether, and the remained substance methoxymethyl-3-cephem-4-carboxylate(syn isomer)(1.0g) chloride in turn, dried and then evaporated to dryness adjusted to pH 2.0 with diluted hydrochloric acid and methoxymethyl-3-cephem-4-carboxylic acid (syn isomer) bicarbonate, water and an aqueous solution of sodium under reduced pressure. The residue was stirred for formamidothiazol-4-yl]-2-methoxyiminoacetamido]-3followed by extracting with an aqueous solution of then extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium formamidothiazol-4-yl)-2-methoxyiminoacetamidol-3o the residue was added ethyl acetate (20 ml), To a cold suspension of tert-butyl 7-[2-(2as collected by filtration to give 7-[2-(2-

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broad s), 3.90 (3H, s), 4.19 (2H, s), NMR &ppm (DMSO-d₆) : 3.22 (3H, s), 3.55 (2H, (1H, s), 9.67 (1H, d, J*8Hz), 12.58 5.17 (1H, d, J.SHz), 5.81 (1H, dd, J=SHz, 8Hz), 7.43 (1H, s), 8.51 IR (Nujol) : 3250, 1780, 1660 cm-1 (1H, broad s)

Example 20

according to the similar manner to that of Example 19. nethoxyiminoacetamido]-3-methylthiomethyl-3-cephem-4carboxylate (syn isomer)(0.9 g) with trifluoroacetic acetamido]-3-methylthiomethyl-3-cephem-4-carboxylic 7-[2-(2-Formamidothiazol-4-yl)-2-methoxyiminoicid (syn isomer)(0.64 g) was obtained o, reacting acid (5.8 g) in the presence of anisole (0.9 ml) tert-butyl 7-[2-(2-formamidothiazol-4-yl)-2-

NMR &ppm (DMSO-d₆) : 1.99 (3H, s), 3.38-4.1 (4H, m), 3.93 (3H, s), 5.25 (1H, d, J=SHz), 5.79 (1H, dd, J*SHz, 8Hz), 7.45 (1H, s), 8.43 (1H, s), 9.65 (1H, d, J-8Hz), IR (Nujol) : 3250, 1780, 1660 cm⁻¹ 12.68 (1H, broad s)

21 and 22 were obtained by reacting tert-butyl ester of the corresponding cephalosporanic acid derivatives with trifluoroacetic acid in the presence of anisole accord-The compounds described in the following Examples ing to the similar manner to that of Example 19.

7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-5-cephem-4-carboxylic acid hydrochloride syn isomer)

IR (Nujol) : 5300, 1780, 1720, 1660, 1640 cm⁻¹ Example 22 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid (syn . IR (Nujol) : 3350, 1770, 1670 cm-1 isomer)

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Example 23

and tetrahydrofuran (2 ml) was added conc. hydrochloric acid to give 7-[2-[2-aminothiazol-4-yl]-2-methoxyiminoacetamido]methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxyl1c diisopropyl ether, the precipitated crystals were collected by filtration, washed with diisopropyl ether and then dried acid (syn isomer) (0.52 g) in a mixture of methanol (3 ml) $(0.18\ g)$, and the mixture was stirred at 30°C for 4 hours. To a suspension of 7-[2-(2-formamidothiazol-4-yl)-2-3-methoxymethyl-3-cephem-4-carboxylic acid hydrochloride After the reaction mixture was cooled and diluted with (syn isomer) (0.45 g).

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IR (Nujol) : 3300, 1780, 1720, 1660, 1640 cm⁻¹ broad s), 4.0 (3H, s), 4.24 (2H, s), NMR 6ppm (DMSO-d₆) : 3.26 (3H, s), 3.58 (2H, 5.24 (1H, d, J=5Hz), 5.82 (1H, dd, J=SHz, 8Hz), 7.01 (lH, s), 9.87 (1H, d, J-8Hz)

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Example 24

(4H, m), 3.88 (3H, s), 5.25 (1H, d, J*5Hz), 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]methylthiomethyl-3-cephem-4-carboxylic acid (syn isomer) 5.78 (1H, dd, J.SHz, 8Hz), 6.82 (1H, s), according to the similar manner to that of Example 23. nixture of methanol (3 ml) and tetrahydrofuran (1 ml) 7.24 (2H, broad s), 9.64 (1H, d, J=8Hz) 3-methylthiomethyl-3-cephem-4-carboxylic acid (syn formamidothiazol-4-yl)-2-methoxyiminoacetamido}-3-(0.6 g) with conc. hydrochloric acid (0.4 g) in a isomer)(0.25 g) was obtained by reacting 7-[2-(2-NMR &ppm (DMSO- d_6) : 2.01 (3H, s), 3.2-4.1 IR (Nujol) : 3350, 1770, 1670 cm⁻¹

Example 25

stirred at -20 to -15°C for 15 minutes. After the reaction 4, N-dimethylformamide (2.92 ml) and phosphorus oxychloride mixture was poured into water, it was extracted with ethyl acetate. The extract was washed with an aqueous solution sulfate. Removal of the solvent gave a residue (13.4 g), in eluent. The fractions containing the desired compound which was chromatographed on silica gel (100 ml) using a was added at -15°C an activated acid, which was prepared mixture of benzene and ethyl acetate (5:1 by volume) as vere collected and then evaporated to dryness to obtain (3.46 ml) in a conventional manner, and the mixture was of sodium bicarbonate and an aqueous solution of sodium benzhydryl 7-[(2-formamidothiazol-4-yl)glyoxylamido]-3chloride, followed by drying over anhydrous magnesium silylacetamide (18.4 g) in methylene chloride (100 ml) from (2-formamidothiazol-4-yl)glycxylic acid (6.56 g), To a solution of benzhydryl 7-amino-5-methylthiomethyl.5-cephem-4-carboxylate (10 g) and trimethyl-

(1H, d, J=5Hz), 5.87 (1H, dd, J=5Hz, N.M.R. Sppm (DMSO-d₆) : 1.83 (3H, s), 3.58 (2H, broad s), 3.67 (2H, broad s), 5.33 8Hz), 6.90 (1H, s), 7.40 (10H, s), I.R. (Nujol) : 3300, 1780, 1700, 1656 cm⁻¹ methylthiomethyl-3-cephem-4-carboxylate (7.1 g)

The following compounds were obtained by reacting 7-amino-3-substituted cephalosporanic acid derivatives with the corresponding acids according to the similar manner to that of Example 25.

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(1H, d, J=8Hz), 12.68 (1H, broad s)

8.47 (1H, s), 8.58 (1H, s), 9.88

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Example 26

7. [(2-Aminothiazol-4-yl)glyoxylamido].3-methylthio--I.R. (Nujol) : 3300, 1762, 1522' cm⁻¹ nethyl-3-cephem-4-carboxylic acid.

7-[2-(2-Aminothiazol-4-yl)-DL-glycinamido]-3-I.R. (Rujol) : 3300, 1755, 1686, 1600 cm⁻¹. methylthiomethyl-3-cephem-4-carboxylic acid. Example 27

To a mixture of benzhydryl 7-amino-3-methylthionethyl-3-cephem-4-carboxylate (4.92 g) and N-tertxample 28

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acetate. This solution was washed with an aqueous solusodium chloride, and then dried over anhydrous magnesium dryness to give a residue, which was dissolved in ethyl (2.39 g), and the mixture was stirred at ambient temperature for an hour. After the insoluble substance was (4.0 g) in methylene chloride (100 ml) and tetrahydroremoved by filtration, the filtrate was evaporated to tion of sodium bicarbonate and an aqueous solution of furan (80 ml) was added N,N'-dicyclohexylcarbodiimide butoxycarbony1-2-(2-formamidothiazol-4-y1)-DL-glycine sulfate. Removal of the solvent gave benzhydryl

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DL-glycinamido] - 5-methylthiomethyl - 5-cephem-4-carboxylate 7.[N-terr-outoxycarbonyl-2-(2-formamidothiazol-4-yl)-

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N.M.R. 6ppm (DMSO-d₆) : 1.36 (9H, s), 1.80 (3H, s), 5.90 (1H, s), 7.13 (1H, s), 7.33 (10H, 5.38 (1H, d, J-8Hz), 5.6-5.9 (1H, m), I.R. (Nujol) : 3300, 1770, 1710, 1680, 1615 cm⁻¹ broad s), 8.47 (lH, s), 9.08 (lH, d, 3.58 (4H, m), 5.16 (d, J=SHz))(1H) 5.25 (d, J=SHz)

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Example 29

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A mixture of 7-[(2-formamidothiazol-4-yl)-

1=8Hz)

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rrystals in the concentrate were collected by filtration with an aqueous solution of sodium bicarbonate and then methanol (50 ml) was stirred at ambient temperature for concentrated under feduced pressure. The precipitated glyoxylamido]-3-methylthiomethyl-3-cephem-4-carboxylic 2 hours. The reaction mixture was adjusted to pH 5-6 nethylthiomethyl-3-cephem-4-carboxylic acid (1.1 g). acid (3.0 g) and conc. hydrochloric acid (3 ml) in to give 7-[(2-aminothiazol-4-yl)glyoxylamido]-3-

(1H, dd, J=SHz, 8Hz), 7.37 (2H, broad s), broad s), 5.22 (1H, d, J.SHz), 5.68 N.M.R. &ppm (DMSO-d₆) : 2.00 (3H, s), 3.65 (4H, 7.83 (1H, s), 9.73 (1H, d, J*8Hz) I.R. (Nujoi) : 3300, 1762, 1522 cm-1

Example 30

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chloride, dried over anhydrous magnesium sulfate and then evaporated to obtain benzhydryl 7-[N-tert-butoxycarbonyl-2-(2-formamidothiazol;4-y1)-DL-glycinamido]-3-methylthiohydrofuran (25 ml) was stirred at 30 to 35°C for 5 hours. The reaction mixture was adjusted to pH 4.5 with sodium solution was washed with an aqueous solution of sodium methyl-3-cephem-4-carboxylate (9.4 g) and conc. hydrochloric acid (4.16 ml) in methanol (100 ml) and tetra-A mixture of benzhydryl 7-[N-tert-butoxycarbonyl-2-(2-aminothiazol-4-yl)-DL-glycinamido]-3-methylthiobicarbonate and then evaporated to dryness to give a residue, which was dissolved in ethyl acetate. This methyl-3-cephem-4-carboxylate (7.4 g).

7.43 (10H, broad s), 8.93 (1H, d, J*8Hz) M.M.R. $\delta ppm \ (DMSO-d_6) : 1.40 \ (9H, s), 1.80 \ (3H, s),$ I.R. (Nujol): 3300, 1772, 1716, 1685, 1623, 1244, 3.6 (4H, m), 3.0-5.4 (2H, m), 5.6-5.9 (2H, m), 6.93 (1H, s), 7.30 (1H, s), 1170, 116C cm⁻¹

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The following compounds were obtained by reacting 7-acylanino-3-substituted cephalosporante acid derivatives having a formamido group with hydrochloric acid eccording to the similar manner to that of Example 30.

7.[2.(2.Aminothiarol-4-yl)-DL-glycinamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid.
1.R. (Nujol): 3300, 1755, 1686, 1600 cm

Example 32
7.(2.(2.Aminothiazol-4-yl).DL-glycolamido]-3methylthiomethyl-3.cephem-4-carboxylic acid.
1.R. (Nujol): 3300, 1752, 1675, 1600 cm⁻¹

Example 33

Enailydry1 7-[(2-formanidothiazol-f-yl]glyoxylanido]--methythiomethyl-3-cephem-4-cextboxylate (7.0 g) was dissolved in a solution of methylene chloride (70 ml), anisole (71 ml) and trifluoroacetic acid (14 ml), and the mixture was stirred at ambient temperature for an hour Atter the solvent was removed by distillation under reduced pressure, the residue was dissolved in water, adjusted to pressure, the residue was dissolved in water, adjusted to the ethyl acetate. The extract was washed with an aqueous sodium chloride and dided over magnesium auflate, followed by evaporation. The residue was pulverized with dissopropyl by evaporation and the dissolved with a contain 7-[(2-formanidothiazol-4-yl)]glyoxylanidol-3-methylthiomethyl-3-cephem-4-carboxylic soid (3.1) g).

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broad s), 5.24 (1H, d, J-5H1), 5.73 (1H, dd, J-5H1, 8H1), 8.43 (1H, s), 8.57 (1H, s), 9.90 (1H, d, J-6H1), 12.80 (1H, broad s)

N.M.R. &ppm (DMSO-d₆) : 2.00 (3H, s), 3.63 (4H,

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The following compounds were obtained by reacting 7-acylamino-3-substituted cephalosporanic acid derivatives having benzhydryl ester with 2,2,2-trifluoroacetic acid in the presence of anisole according to the similar manner to that of Example 33.

Example 34

7-[(2-Aminothiazol-4-yl)glyoxylamido]-3-methylthio-methyl-3-cephem-4-carboxyltc acid.

I.R. (Nujo1) : 3300, 1762, 1522 cm⁻¹

Example 35

7-[2-(2-Aminothiazo1-4-y1)-U.-81ycolamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid.
1.R. (Nujol): 3300, 1752, 1675, 1600 cm⁻¹

Example 36

(2-aminothiazol-4-yl)-DL-glycinamido]-3-methylthiomethyl-3-cephem-4-carboxylate (7.0 g), anisole (7 ml) and 2,2,2trifluoroacetic acid (21 ml) was stirred at 5°C for half tion resin "Diajon HP.20" (Trade Mark, made by Mitsubishi A mixture of benzhydryl 7-[N-tert-butoxycarbonyl-2remained aqueous solution was adjusted to pH 4.2 with 5% aqueous solution was chromatographed on nonionic adsorpwater (250 ml), elution was carried out with 30% aqueous isopropyl alcohol. The fractions containing the desired compound were collected and then evaporated, followed by stance was collected by filtration and then washed with of ethyl acetate (50 ml) and water (100 ml). After the dilsopropyl ether, followed by dissolving in a mixture the aqueous layer was completely removed, and then the aqueous solution of sodium bicarbonate. The resultant Chemical Industries Ltd.)(100 ml). After washing with aqueous layer was separated out, the ethyl acctate in an hour. To the reaction mixture was added dropwise diisopropyl ether (300 ml), and the precipitated sub-

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lyophilization to obtain 7-{2-(2-aminothiazol-4-yl)-DL-8lycinamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid (2.9 g).

(4H, m), 5.27 (1H, d, J=5Hz), 5.50 N.M.R. 6ppm (D,0+DC1) : 2.07 (3H, s), 3.5-4.0 1.R. (Nujol) : 3300, 1755, 1686, 1600 cm-1 (1H, s), 5.60 (d, J*SH2) 5.72 (d, J*SH2))(1H), 7.27 (1H, s)

xample 37

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followed by lyophilization to obtain 7-[2-(2-aminothiazol-(150 mg) at 5 to 10°C , and the mixture was stirred at the [1.1 g] in methanol (80 ml) was added sodium borohydride water (100 ml), elution was carried out with 30% aqueous isopropyl alcohol. The fractions containing the desired queous solution was chromatographed on nonionic adsorpcompound were collected and then evaporated to dryness, residue was added water (50 ml), followed by adjusting ion resin "Diaion HP-20" (50 ml). After washing with same temperature for half an hour. After the reaction acid, the solvent was removed by distillation. To the To a solution of 7-[(2-aminothiazol-4-yl)glyoxylto pH 5.0 with 10% hydrochloric acid. The resultant nixture was adjusted to pH 5.0 with 101 hydrochloric amido]-3-methylthiomethyl-3-cephem-4-carboxylic acid -yl).DL-glycolamido].3-methylthiomethyl.3-cephem-4carboxylic acid (0.75 g).

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N.M.R. & ppm (DMSO-d;) : 2.00 (3H, s), 3.48 (2H, (2H, broad s), 8.33 (d, J=8Hz) 8.42 (d, J=8Hz))(1H) broad s), 5.67 (2H, broad s), 4.93 5.57 (1H, m), 6.50 (1H, s), 7.03 1.R. (Nujol) : 3300, 1752, 1675, 1600 cm⁻¹ (1H, s), S.07 (1H, d, J. SHz),

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chloride (1.23 ml) and N,N-dimethylformamide (1.1 ml) was suspended in dry tetrahydrofuran (40 ml). To the Vilsmeier reagent prepared from phosphorus oxysuspension was added 2-(2-formamidothiazol-4-yl)-2-

- 5-cephem-4-carboxylate (4.66 g) and trimethylsilylacetamide tert-butoxycarbonylmethoxyiminoacetic acid (syn isomer) at -20°C at a time, and the mixture was stirred at the the other hand, benzhydryl 7-amino-3-methylthiomethyl-(4.0 g) under ice-cooling with stirring, and the mix-(8.6 g) were dissolved in methylene chloride (50 ml). To the solution was added the activated acid solution minutes to prepare the activated acid solution. ure was stirred at the same temperature for 50
 - outoxycarbonylmethoxyiminoacetamido]-3-methylthiomethylsodium chloride, and then dried over magnesium sulfate, followed by evaporation under reduced pressure to give solution, and the organic layer was separated, washed 3-cephem-4-carboxylate (syn isomer)(8.0 g), mp 132cthyl acetate (200 ml) were added to the resultant same temperature for an hour. Water (100 ml) and with 5% aqueous sodium bicarbonate and an aqueous benzhydryl 7-[2-(2-formamidothiazol-4-yl)-2-tert-12
- 3.60 (2H, broad s), 3.66 (2H, broad s), 4.98 \$ppm (DMSO-d6, 6): 1.47 (9H, s), 1.83 (3H, s), 7.4 (10H, m), 7.48 (1H, s), 8.54 (1H, s), 5.92 (1H, dd, J=SHz, 8Hz), 6.95 (1H, s), (2H, broad s),5.32 (1H, d, J=5Hz), 1R (Nujol) : 3260, 1783, 1725, 1687 cm-1

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3.63 (1H, d, J=8Hz), 12.65 (1H, broad s)

methylthiomethyl-3-cephem-4-carboxylate (syn isomer) Benzhydryl 7-[2-(2-formamidothiazol-4-yl)-2benzhydryloxycarbonylmethoxyiminoacetamido]-3-

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(7.8 g) was obtained by reacting benzhydryl 7-amino-3-methylthiomethyl-3-cephom-4-carboxylate (4.0 g)

methoxyiminoacetic acid (syn isomer)(6.18 g), phosphorus oxychloride (1.42 ml) and N,N-dimethylformamide (1.21 ml), according to a similar manner to that of Example with the activated acid solution prepared from 2-(2formamidothiazol-1-yl)-2-benzhydryloxycarbonyl-38, mp 135-142°C.

6.98 (111, s), 7.37 (20H, m), 7.50 (1H, s), 5.98 (1H, dd, J=5Hz, 8Hz), 6.95 (1H, s), NMR &ppm (DMSO-d6) : 1.83 (3H, s), 3.63 (4H, m), 5.0 (2H, broad s), 5.35 (1H, d, J=5Hz), IR (Nujo1) : 3250, 1780, 1722, 1685 cm⁻¹

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8.57 (1H, s), 9.82 (1H, d, J=8Hz),

12.73 (1H, broad s)

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N.N-dimethylformamide (0.75 ml), according to a similar 5.86 (1H, dd, J=5Hz, 8Hz), 6.84 (1H, s), 2-(2-(2,2,2-trifluoroacetamido)thiazol-4-yl}acetamido]-MAR &ppm (DNSO-d6) : 2.00 (3H, s), 3,56 (4H, m), Benzhydryl 7-[2-benzhydryloxycarbonylmethoximino-3-methylthiomethyl-3-cephem-4-carboxylate (syn isomer) isomer)(3.68 g), phosphorus oxychloride (0.89 ml) and 6.88 (1H, s), 7.3 (20H, m), 9.62 (1H, (5.6 g) was obtained by reacting benzhydryl 7-amino-IR (Nujol) : 3300, 1786, 1733, 1675, 1610 cm⁻¹ 4.84 (2H, s), 5.26 (1H, d, J=SH1), 3-methylthiomethyl-3-cephem-4-carboxylate (3.0 g) with the activated acid solution prepared from 2trifluoroacetamido)thiazol-4-yl}acetic acid (syn benzhydryloxycarbonylmethoximino-2-[2-(2,2,2manner to that of Example 38, mp 165-169°C.

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To a suspension of benzhydryl 7-[2-(2-Example 41

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d, J-8Hz)

Formamidothlazol-4-yl)-2-tert-

outoxycarbonylmethoxyiminoacetamido]-3-methylthiomethyl-(160 ml) was added conc. hydrochloric acid (5,6 ml), and the mixture was stirred at 35°C for an hour.

saturated aqueous sodium bicarbonate. After distilling 3-cephem-4-carboxylate (syn isomer)(8.0 g) in methanol methanol under reduced pressure, the residue was dis-The resultant solution was adjusted to pH 5.0 with a solved in water (100 ml) and ethyl acetate (200 ml).

aqueous sodium chloride and dried over magnesium sulfate. 3-cephem-4-carboxylate (syn isomer)(7.0 g), mp 140-145°C. butoxycarbonylmethoxyiminoacetamido]-3-methylthiomethyl-The ethyl acetate layer was washed with a saturated The solvent was removed by filtration to give IR (Nujol) : 3250, 1780, 1723, 1680 cm⁻¹ benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-tert-2 07

5.29 (1H, d, J=5Hz), 5.87 (1H, dd, J=5Hz, NNR 6ppm (DMSO-d6) : 1.43 (9H, s), 1.83 (3H, s), BHz), 6.83 (1H, 3), 6.95 (1H, S), 3.63 (4H, m), 4.6 (211, broad s), 20

Example 42

benzhydryloxycarbonylmethoxyiminoacetamido]-3-Benzhydryl 7-[2-(2-aminothiazol-4-y1)-2-

7.4 (10H, m), 9.52 (1H, d, J=8Hz)

methylthiomethyl.3-cephem-4-carboxylate (syn isomer) methylthiomethyl-3-cephem-4-carboxylate (syn isomer) (7.0 g); mp 148-155°C, was obtained by reacting benzhydryloxycarbonylmethoxyiminoacetamido]-3benzhydryl 7-[2-(2-formamidothiazol-4-yl)-2-25

NNR &ppm (DNSO-d6) : 1.83 (311, s), 3.60 (4H, m), 4.90 (2H,broad s), 5.30 (1H, d, J=5Hz), (7.5 g) with conc, hydrochloric acid (3.9 ml) according to a similar manner to that of Example 41. 30

6.93 (1H, s), 6.97 (1H, s), 7.4 (20H, m), 5.87 (III, dd, J=SIIZ, 8Hz), 6.86 (1H, s), 9.67 (1H, d, J=8Hz). 35

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7-[2-carboxymethoxyimino-2-(2-aminothiazol-4-yl)acetamido]methylthiomethyl-3-cephem-4-carboxylic acid (syn isomer) The resultant solution was adjusted to pll 2.0 with conc. filtration and dried over phosphorus pentoxide to give hydrochloric acid. The precipitates were collected by A solution of 7-[2-carboxymethoxyimino-2-{2-(2, [4.1 g) and sodium acetate (9.56 g) in water (41 ml) 3-methylthiomethyl-3-cephem-4-carboxylic acid (syn vas stirred for 19.5 hours at ambient temperature, 2,2-trifluoroacetamido)thiazol-4-yl)acetamido]-3isomer)(1.8 g), mp 173-176°C (dec.).

1H, dd, J=SHz, BHz),6.77 (111; s),9.45 (111, d, J=BHz) 4.60 (2H, broad s), 5.17 (1H,d,J-5Hz), 5.73 NMR 6ppm (DMSO-d6) : 2.00 (3H, s), 3.57 (4H, m), IR (Nujol) : 3370, 1772, 1670 (broad) cm-1

7- [2-carboxymethoxyimino-2-{2-(2,2,2-trifluoroacetamido)carboxylic acid (syn isomer)(4.2 g), mp 183-186°C (dec.). nethylene chloride (11.2 ml) was added trifluoroacetic thiazol-4-yl}acetamido]-3-methylthiomethyl-3-cephem-4carboxylate (syn isomer)(5.6 g) and anisole(5.6 ml) in 1.5 hours at ambient temperature and then poured into a mixture of disopropyl ether (400 ml) and petroleum carbonylmethoxyimino-2-(2-(2,2,2-trifluoroacetamido)icid (11.2 ml) at 10°C. The mixture was stirred for chiazol-4-yl)acetamido|-3-methylthiomethyl-3-cephem-4-To a solution of benzhydryl 7-[2-benzhydryloxyther (100 ml). The precipitates were collected by filtration and washed with petroleum ether to give NMR 6ppm (DMSO-d6):2.00 (3H,s), 3.62 (4H, m), 4.70 (2H, s), 5.24 (111, d, J=511z), IR (Nujol) : 3300, 1778, 1723, 1660 cm-1

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What we claim is:

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H: A compound of the formula:
$$R^{1-A-COHH} \longrightarrow R^{2}$$

in which R¹ is a group of the formula;

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 R^3 is carboxy or a protected carboxy group, thiomethyl or lower alkenylthiomethyl, wherein R^4 is lower alkyl and R^5 is amino or a protected amino group, R² is lower alkoxymethyl, lower alkyl-

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- "N~OR6, wherein R6 is hydrogen, lower alkenyl, of amino, a protected amino group, hydroxy, is lower alkylene which may have a substilower alkynyl, lower alkyl, or lower alkyl selected from carboxy, a protected carboxy tuent selected from the groups consisting group, amino, a protected amino group and substituted by one or more substituent(s) oxo and a group of the formula;
 - a pharmaceutically acceptable salt thereof. a heterocyclic group, and A compound of claim 1, in which . .
 - the formula: R¹-A- is a group of the formula:

in which R¹ is a group of the formula:

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5.80 (1H, dd, J-SHz, 8Hz), 7.60 (1H, s),

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 $R^{5} \mathcal{H}_{c} \mathcal{V}_{c}$, wherein R^{5} is amino or acylamino,

. R⁶ is lower alkyl, carboxy(lower)alkyl or esterified carboxy(lower)alkyl, and ${\sf R}^3$ is carboxy or an esterified carboxy group. 4 compound of claim 2, which is syn isomer. compound of claim 3, in which

compound of claim 4, in which

S is amino,

'n

is lower alkox; methyl or lower alkylthiomethyl, is lower alkyl or carboxy(lower)alkyl. R³ is carboxy, and

7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido}-A compound of claim 5, which is selected from the group consisting of:

7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid or its 3-methylthiomethyl.3-cephem-4-carboxylic acid,

acetamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid. 7-[2-(2-aminothiazol-4-y1)-2-carboxymethoxyiminohydrochloride, and

wherein R⁵ is amino or acylamino, R is a g*oup of the formula: NS X N

A compound of claim 1, in which

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A is methylene, aminomethylene, acylaminomethylene, hydroxymethylene or carbonyl, and

is carboxy or an esterified carboxy group, compound of claim 7, in which is amino.

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is lower alkylthiomethyl, and compound of claim 8, in which

A compound of claim 9, which is selected from the group consisting of: R3 is carboxy.

'- [2-(2-aminothiazol-4-yl)acetamido]-3-methylthiomethyl--[2-(2-aminothiazol-4-yl)glycinamido]-3-methyl-'-[2-(2-aminothiazol-4-yl)glycolamido]-3-methylhiomethyl-3-cephem-4-carboxylic scid, 5-cephem-4-carboxylic acid,

7-[2-(2-aminothiazol-4-yl)glyoxylamido]-3-methylthiomethyl-3-cephem-4-carboxylic acid and thiomethy1-3-cephem-4-carboxylic acid.

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wherein R⁴ is as defined in claim 1, A compound of claim 1, in which R¹ is a group of the formula:

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A is aminomethylene or acylaminomethylene, and ${\tt R}^3$ is carboxy or an esterified carboxy group.

R4SO2NH, wherein R4 is as defined above. A compound of claim 11, in which R¹ is a group of the formula:

12.

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A compound of claim 13, which is selected from A compound of claim 12, in which 3 is carboxy. 7

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13,

7-[2-(3-methanesulfonamidophenyl)glycinamido]-3-7-[2-(3-methanesulfonamidophenyl)glycinamido]-3nethylthiomethyl-3-cephen-4-carboxylic acid, the group consisting of:

7-[2-(3-methanesulfonamidophenyl)glycinamido]-3-7-[2-(3-methanesulfonamidophenyl)glycinamido]-3allylthiomethyl-3-cephem-4-carboxylic acid or methoxymethyl-3-cephem-4-carboxylic acid and thylthiomethyl.3-cephem-4-carboxylic acid, its trifluoroacetate

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A process for preparing a compound of the formula: 35

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in which \mathbb{R}^l is a group of the formula:

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 \mathbb{R}^3 is carboxy or a protected carboxy group thiomethyl or lower alkenylthiomethyl, ${\rm R}^2$ is lower alkoxymethyl, lower alkyl-

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consisting of amino, a protected amino group, hydroxy, oxo and a group of the substituent selected from the groups A is lower alkylene which may have a

*N-OR6, wherein R6 is hydrogen, lower alkenyl, lower alkynyl, lower alkyl, or lower alkyl substituted by one or carboxy, a protected carboxy group, more substituent(s) selected from

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and pharmaceutically acceptable salt thereof, heterocyclic group, which comprises.

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amino, a protected amino group and a

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(1): reacting a compound of the formula:
$$H_2N \xrightarrow{} F^S \longrightarrow R^2$$

35

in which R² and R³ are each as defined above, or its reactive derivative at the amino group or a salt thereof with a compound of the formula: -101-

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or a salt thereof to give a compound of the formula: in which R¹ and A are each as defined above, or its reactive derivative at the carboxy group R1-A-CONH

in which R¹, R², R³ and A are each as defined or a salt thereof; or

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amino group, and $3 are each as defined above, in which A¹ is lower alkylene having a protected

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group, and $R^{\frac{1}{3}}$ are each as defined above, in which A² is lower alkylene having an amino or a salt thereof; or

(3) subjecting a compound of the formula:

 $R_{a}^{1} \cdot A \cdot CONH_{a} = \frac{R^{2}}{N}$ In which R_{a}^{1} is a group of the formula: $R^{2} + \frac{R^{2}}{N} = 0$ or $R^{2} + \frac{R^{2}}{N} = 0$

wherein R⁸ is a protected amino group,

10

amino-protective group to give a compound of the R², R³ and A are each as defined above, or a salt thereof to removal reaction of the

formula:
$$R_{b}^{1} \cdot A \cdot CONH \xrightarrow{T} R^{2}$$

 R^{\star} in which R^{l}_{b} is a group of the formula:

$$H_2N + \frac{N}{\xi}$$
 or $H_2N + \frac{N}{\xi}$, and $K_1 + \frac{N}{\xi}$ as all thereof; or

(4) subjecting a compound of the formula: or a salt thereof; or

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in which a is a protected carboxy group, and R¹, R² and A are each as defined above. carboxy-protective group to give a compound of or a salt thereof to removal reaction of the

33

32

in which R¹, R² and A are each as defined above, or a salt thereof; or

(5) introducing a carboxy-protective group into a compound of the formula:

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or a salt thereof to give a compound of the formula: in which R1, R2 and A are each as defined above,

in which R^1 , R^2 , R^3_a and A are each as defined or a salt thereof; or

6 reducing a compound of the formula:

in which A. is lower alkylene having an oxo

group, and R^1 , R^2 and R^3 are each as defined or a salt thereof to give a compound of the

group, and R^1 , R^2 and R^3 are each as defined above, reacting a compound of the formula:

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In which A^5 is lower alkylene which may have a group of the formula: "N~OR", wherein R6 is as defined above,

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or a salt thereof with a compound of the formula; χ^{1} is halogen, and R^{2} and R^{3} are each as defined above,

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in which R⁵ is as defined above, to give a compound of the formula:

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in which R2, R3, R5 and A5 are each as defined above,

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subjecting a compound of the formula: or a salt thereof; or 3

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$$R^{1}-A^{6}$$
-CONH \longrightarrow S R^{2} R^{2}

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in which A⁶ is lower alkylene having a group of the formula: £04-

protected carboxy group, and \mathbb{R}^1 , \mathbb{R}^2 and \mathbb{R}^3 are each as defined above, or a salt thereof to removal reaction of the carboxy-protective group to give a compound wherein R_a^6 is lower alkyl substituted by of the formula:

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in which A is lower alkylene having a group of the formula:

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stituted by carboxy, and R^1 , R^2 and R^3 are each as defined = $N \sim OR_b^6$, wherein R_b^6 is lower alkyl sub-

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subjecting a compound of the formula: or a salt thereof; or

$$R^1$$
-A-CONH R^2 -R²

 R_b^3 in which R_b^3 is lower alkoxycarbonyl substituted by protected amino and protected carboxy groups, and

33

$$R_1$$
, R^2 and A are each as defined above,

amino- and carboxy-protective groups to give a or a salt thereof to removal reaction of the compound of the formula;

2

stituted by amino and carboxy, and $$\rm R^1$, $\rm R^2$ and A are each as defined above, in which R is lower alkoxycarbonyl subor a salt thereof, or

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amino and protected carboxy groups, protected carboxy groups or lower in which A⁸ is lower alkylene having a group stituted by protected amino and alkoxycarbonyl(lower)alkyl subalkyl substituted by protected of the formula: "N.ORC, wherein Ro is lower

and R^{1} , R^{2} and R^{3} are each as defined above, amino- and carboxy-protective groups to give a or a salt thereof to removal reaction of the compound of the formula:

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by amino and carboxy, and R^1 , R^2 and R^3 are each as defined above, of the formula: "N-ORd", wherein Rd is lower alkoxycarbonyl(lower)carboxy or lower alkyl substituted in which A is lower alkylene having a grdup alkyl substituted by amino and or a salt thereof; or

introducing a carboxy-protective group into a compound of the formula: (17)

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in which R1, R2, R3 and A7 are each as deor a salt thereof to give a compound of the fined above,

$$R^{\frac{1}{2}-A^6-CONH}\prod_0^{R^2}R^2$$

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in which R1, R2, R3 and A6 are each as reacting a compound of the formula: or a salt thereof; or defined above,

(17)

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STATE OF THE STATE

$$R^{1}-A^{10}-CONH \xrightarrow{S} R^{2}$$

formula: () and R³ are each as defined substituted by a group of the group of the £grmula: "N~OR in which A 10 is lower alkylene having a wherein R_e is lower alkyl

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or a salt thereof with a compound of the

to give a compound of the formula: in which R7 is lower alkyl,

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wherein Rf is lower alkyl subgroup of the formula: "N~OR¢ in which All is lower alkylene having a

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stituted by a group of the formula:

R1, R2 and R3 are each as defined above, wherein R⁷ is as defined above,

S

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(13) reacting a compound of the formula: or a sait thereof; or

$$R^{1}-A^{11}-COMI_{1}-R^{2}-R^{2}$$

$$COOII$$
in which R^{1} , R^{2} and A^{11} are each as defined above,
or a salt thereof with a base to give a compound of the formula:

admixture with pharmaceutically acceptable carriers. R^1 and R^2 are each as defined above, A pharmaceutical composition comprising, as active ingredients, the compounds of the claim 1, in or a salt thereof.

administering a compound of the claim 1 to infected A method for treating an infectious disease caused y pathogenic microorganisms, which comprises human being and animals.

$$R^{A}$$
 CH₂S- R^{b} .

2

in which Ra, Rb' and R3 are each as defined above,

reducing a compound of the formula:

(3) 15

or a salt thereof; or

and a salt thereof,

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which comprises

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formula:

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Rb'-SH

to give a compound of the formula;

CH2S-Rb'

2

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defined above,

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3.8

or a salt thereof to removal reaction of the amino-protective group to give a compound of the formula: above,

in which Rb' and R3 are each as defined above, or a salt thereof.